

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROVOCHOLINE® safely and effectively. See full prescribing information for PROVOCHOLINE.

PROVOCHOLINE® (methacholine chloride) powder for solution, for oral inhalation

Initial U.S. Approval: 1986

### WARNING: SEVERE BRONCHOCONSTRICTION

See full prescribing information for complete boxed warning.

- Severe bronchoconstriction can result from the Provocholine administration (including the lowest dose) (5.1)
- Use of Provocholine is contraindicated in pediatric and adult patients with baseline FEV<sub>1</sub> <60% predicted or adults with FEV<sub>1</sub> <1.5 L (5.1)
- Use of Provocholine is not recommended in patients with clinically apparent asthma or wheezing (5.1)
- If severe bronchoconstriction occurs, reverse immediately with a rapid-acting inhaled bronchodilator agent (β-Agonist) (5.1)

### INDICATIONS AND USAGE

Provocholine is a cholinergic agonist indicated for the diagnosis of bronchial airway hyperreactivity (methacholine challenge test) in adults and pediatric patients five years of age and older who do not have clinically apparent asthma (1)

### DOSAGE AND ADMINISTRATION

- Provocholine is a potent bronchoconstrictor. Do not inhale the powder. Do not handle this material if you have asthma or hay fever (2.1)
- The methacholine challenge test should be conducted in a pulmonary function laboratory or clinic, by adequately trained personnel, for safety and accuracy (2.2)
- Assess baseline FEV<sub>1</sub> values prior to Provocholine use (2.4)
- Administer using either the 5-Breath Dosimeter Dosing Method or the 2-Minute Tidal Breathing Dosing Method with the doubling or quadrupling stepwise protocols (2.3, 2.4)
- See the Full Prescribing Information for the required reconstitution and dilution procedures prior to use (2.5)
- See the Full Prescribing Information for the calculation and interpretation of the results (2.6)

### DOSAGE FORMS AND STRENGTHS

Provocholine Powder for Solution: 100 mg in amber glass vials (3)

### CONTRAINDICATIONS

- Known hypersensitivity to methacholine chloride or other parasympathomimetic agents (4)
- Baseline FEV<sub>1</sub> <60% predicted (adults or children) or <1.5 L (adults) (4)

### WARNINGS AND PRECAUTIONS

Healthcare provider and any other personnel involved in the administration of the methacholine challenge test should take precautions to minimize inhalation of Provocholine powder and aerosol (5.2)

### ADVERSE REACTIONS

Adverse reactions associated with Provocholine include headache, throat irritation, light-headedness and itching (6)

To report SUSPECTED ADVERSE REACTIONS, contact Methapharm Inc. at toll-free phone 1-800-287-7686 extension 7804 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- *Beta-Adrenergic Blockers*: May impair reversal of Provocholine-caused bronchoconstriction (7)
- *Beta-Agonists, Anticholinergics, and Theophylline*: Inhibit response to Provocholine; therefore, hold these drugs prior to Provocholine use (7)
- *Oral or Inhaled Corticosteroids, and Inhaled Cromoglycate*: May decrease response to Provocholine (7)

### USE IN SPECIFIC POPULATIONS

*Pregnancy*: Provocholine is not recommended (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2019

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## FULL PRESCRIBING INFORMATION

### WARNING: SEVERE BRONCHOCONSTRICTION

Severe bronchoconstriction can result from Provocholine administration (including the lowest dose). The use of Provocholine is contraindicated in pediatric and adult patients with baseline FEV<sub>1</sub> <60% predicted or adults with FEV<sub>1</sub> <1.5 L. Because of the potential for severe bronchoconstriction, the use of Provocholine in patients with clinically apparent asthma or wheezing is not recommended [see *Warnings and Precautions (5.1)*].

Emergency equipment and medication should be immediately available to treat acute respiratory distress. If severe bronchoconstriction occurs, reverse immediately with a rapid-acting inhaled bronchodilator agent ( $\beta$ -agonist) [see *Warnings and Precautions (5.1)*].

If baseline spirometry is not performed or measured inaccurately, the initial FEV<sub>1</sub> may be underestimated. In this situation, decreases in FEV<sub>1</sub> may not be detected after administration of escalating Provocholine doses, which may result in administration of unnecessary higher doses and an increased risk for excessive bronchoconstriction [see *Warnings and Precautions (5.1)*].

## 1 INDICATIONS AND USAGE

Provocholine is indicated for the diagnosis of bronchial airway hyperreactivity (methacholine challenge test) in adults and pediatric patients five years of age and older who do not have clinically apparent asthma.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Handling Instructions

Given that Provocholine is a potent bronchoconstrictor:

- Provocholine is contraindicated in pediatric and adult patients with or baseline FEV<sub>1</sub> <60% predicted or in adults with FEV<sub>1</sub> < 1.5 L [see *Contraindications (4) and Warnings and Precautions (5.1)*]
- Use of Provocholine is not recommended in patients with clinically apparent asthma or wheezing
- Discard any unused solution from the nebulizer after each administration.

## 2.2 Important Administration Instructions

Provocholine (the methacholine challenge test) should be administered in a pulmonary function laboratory or clinic, by adequately trained personnel, for safety and accuracy, and should be performed only under the responsibility of a healthcare practitioner trained in and thoroughly familiar with all aspects of the technique of methacholine challenge test and the management of respiratory distress. Emergency medication and equipment should be immediately available to treat acute respiratory distress.

Only consider Provocholine use in patients on chronic asthma drugs if the accuracy of the asthma diagnosis is in doubt. In these patients, only administer Provocholine if spirometry is normal after withdrawal of the asthma drugs under supervision.

Before using Provocholine, perform baseline pulmonary function tests with the 0.9% saline diluent or 0.9% saline with the 0.4% phenol diluent (use the same diluent to reconstitute the Provocholine powder) [see *Dosage and Administration (2.3, 2.4)*].

May use Provocholine with or without meals.

Administer Provocholine by oral inhalation using either the 5-Breath Dosimeter Dosing Method or the 2-Minute Tidal Breathing Dosing Method with the doubling or quadrupling stepwise protocols [see *Dosage and Administration (2.3, 2.4)*].

## 2.3 Five (5)-Breath Dosimeter Dosing Method in Patients 5 Years of Age and Older

Administer the diluent prior to administering the Provocholine dose(s) to obtain baseline FEV<sub>1</sub> values. Administer the diluent via oral inhalation and the Provocholine oral inhalation dose(s) using a five-breath dosimeter.

### Administration of the Diluent to Obtain Baseline FEV<sub>1</sub> Values

1. Using a 3 mL syringe and needle, draw up 2 mL of the diluent (0.9% saline or 0.9% saline with 0.4% phenol) and dispense into the nebulizer using a sterile bacterial-retentive filter (porosity 0.22 µm).
2. Instruct the patient to hold the nebulizer upright with the mouthpiece in his/her mouth. The patient should wear a noseclip while inhaling from the nebulizer.
3. At end exhalation during tidal breathing (functional residual capacity), instruct the patient to inhale slowly and deeply through the mouthpiece. Trigger the dosimeter soon after oral inhalation begins. Encourage the patient to continue inhaling slowly (about 5 seconds to complete the inhalation) and to hold the breath at total lung capacity (TLC) for another 5 seconds.
4. Repeat Step 3 for a total of five inspiratory capacity inhalations. Take no more than 2 minutes to perform these 5 inhalations.
5. Perform spirometry and measure the FEV<sub>1</sub> 30 and 90 seconds after the fifth inhalation from the nebulizer. These values may be left at ambient (spirometer) temperature pressure saturated (ATPS). If the FEV<sub>1</sub> value is not of acceptable quality repeat the procedure (patient must have a baseline FEV<sub>1</sub> of ≥ 60% of the predicted value).

### Administration of Provocholine (Methacholine Challenge Testing)

- Using a 3 mL syringe and needle, draw up the recommended Provocholine oral inhalation dose (see Table 1) using the quadrupling dose and dispense into the nebulizer using a sterile bacterial-retentive filter (porosity 0.22 µm). See Table 4 for preparation of the Provocholine solutions for the quadrupling method.

**Table 1: Recommended Provocholine Oral Inhalation Dose(s) [Quadrupling Dose(s)]**

<b>Provocholine Concentration</b>
0.0625 mg/mL (Solution 5)
0.25 mg/mL (Solution 4)
1 mg/mL (Solution 3)
4 mg/mL (Solution 2)
16 mg/mL (Solution 1)

- Repeat steps 2 through 5 for each Provocholine dose, emptying the nebulizer between each dose. To keep the cumulative effect of Provocholine relatively constant, the time interval between the commencement of two subsequent concentrations should be kept to 5 minutes. Stop dosing if the FEV<sub>1</sub> has fallen by ≥ 20% from the mean baseline, the FEV<sub>1</sub> is ≤ 1.5 liters in adults, or the highest Provocholine dose (16 mg/mL) has been administered (whichever comes first). For severe bronchoconstriction, see *Warnings and Precautions (5.1)*. Do not administer additional Provocholine doses.
- After the test is completed, administer an inhaled β-agonist to the patient to expedite the return of the FEV<sub>1</sub> to within 90% of baseline and to relieve any discomfort (the majority of patients revert to normal pulmonary function within 5 minutes after β-agonist administration; in contrast the majority of patients revert to normal pulmonary function within 30-45 minutes without a β-agonist administration). Wait 10 minutes and measure the FEV<sub>1</sub> and Vital Capacity. Patients should not be allowed to leave the laboratory until their FEV<sub>1</sub> has returned to within 90% of baseline.
- After the test, wash and clean reusable nebulizers thoroughly according to manufacturer's recommendations.

## 2.4 Two (2)-Minute Tidal Breathing Dosing Method in Patients 5 Years of Age and Older

Administer the diluent prior to administering the Provocholine dose(s) to obtain baseline FEV<sub>1</sub> values. Administer the diluent via oral inhalation and the Provocholine oral inhalation dose(s) using the English Wright nebulizer or other suitable nebulizers as long as the device output and particle size are characterized.

### Administration of the Diluent to Obtain Baseline FEV<sub>1</sub> Values

1. Using a 3 mL syringe and needle, draw up 2 to 3 mL of the diluent (0.9% saline or 0.9% saline with 0.4% phenol) and dispense into the nebulizer using a sterile bacterial-retentive filter (porosity 0.22 µm).
2. Keeping the nebulizer well away from the patient, adjust the flow meter so that the nebulizer is operating at the calibrated output (0.13 mL/minute time for the English Wright nebulizer).
3. Apply a nose clip and place the face mask loosely over the nose and mouth (or the mouthpiece in the mouth).
4. Start the nebulizer (holding in upright) and start the stopwatch immediately. Instruct the patient to hold the nebulizer to avoid warming the solution.
5. Instruct the patient to relax and breathe the aerosol quietly (tidal breathing) for 2 minutes of inhalation time.
6. After exactly 2 minutes, remove the face mask (or the mouthpiece from the mouth), turn off the flow meter, and discard any remaining solution.
7. Perform spirometry and measure the FEV<sub>1</sub> 30 and 90 seconds after the end of the inhalation. These values may be left at ambient (spirometer) temperature pressure saturated (ATPS). If the FEV<sub>1</sub> value is not of acceptable quality repeat the procedure (patient must have a baseline FEV<sub>1</sub> of ≥ 60% of the predicted value).

### Administration of Provocholine (Methacholine Challenge Test)

8. Using a 3 mL syringe and needle, draw up the recommended Provocholine oral inhalation dose (see Table 2) using either the doubling or quadrupling method and dispense into the nebulizer using a sterile bacterial-retentive filter (porosity 0.22 µm). See Tables 3 and 4 for preparation of the Provocholine solutions for the doubling and quadrupling methods, respectively.

**Table 2: Recommended Provocholine Oral Inhalation Dose(s) By Nebulization [Doubling Dose(s) or Quadrupling Dose(s)]**

<b>Doubling Dose Increments</b>	
<b>Provocholine Concentration</b>	<b>Provocholine Dose*</b>
0.0625 mg/mL (Solution I)	1.484 mcg
0.125 mg/mL (Solution H)	2.969 mcg
0.25 mg/mL (Solution G)	5.938 mcg
0.5 mg/mL (Solution F)	11.875 mcg
1 mg/mL (Solution E)	23.75 mcg
2 mg/mL (Solution D)	47.5 mcg
4 mg/mL (Solution C)	95 mcg
8 mg/mL (Solution B)	190 mcg
16 mg/mL (Solution A)	380 mcg
<b>Quadrupling Dose Increments</b>	
<b>Provocholine Concentration</b>	<b>Provocholine Dose*</b>
0.0625 mg/mL (Solution 5)	1.484 mcg
0.25 mg/mL (Solution 4)	5.938 mcg
1 mg/mL (Solution 3)	23.75 mcg
4 mg/mL (Solution 2)	95 mcg
16 mg/mL (Solution 1)	380 mcg

\* Dose delivered based on the drug output of the English Wright Nebulizer and the duration of inhalation (2 minutes).

9. Repeat steps 2 through 7 for each Provocholine dose, emptying the nebulizer between each dose. However, stop dosing if the FEV<sub>1</sub> has fallen by  $\geq 20\%$  from the mean baseline, the FEV<sub>1</sub> is  $\leq 1.5$  liters in adults, or the highest Provocholine dose (380 mcg) has been administered (whichever comes first). For severe bronchoconstriction, see *Warnings and Precautions (5.1)*. Do not administer additional Provocholine doses.
10. After the test is completed, administer an inhaled  $\beta$ -agonist to the patient to expedite the return of the FEV<sub>1</sub> to within 90% of baseline and to relieve any discomfort (the majority of patients revert to normal pulmonary function within 5 minutes after  $\beta$ -agonist administration; in contrast the majority of patients revert to normal pulmonary function within 30-45 minutes without a  $\beta$ -agonist administration). Wait 10 minutes and measure the FEV<sub>1</sub> and Vital Capacity. Patients should not be allowed to leave the laboratory until their FEV<sub>1</sub> has returned to within 90% of baseline.
11. After the test, wash and clean reusable nebulizers thoroughly according to manufacturer's recommendations and discard disposable nebulizers appropriately.

## **2.5 Reconstitution and Dilution Prior to Administration and Storage of Solutions**

Provocholine requires reconstitution before use (see Tables 3 and 4):

- Add 6.25 mL of 0.9% Sodium Chloride Injection (0.9% saline) OR 0.9% Sodium Chloride Injection with 0.4% phenol (0.9% saline with 0.4% phenol) to the supplied vials containing 100 mg of Provocholine powder
- Shake the vial to obtain a clear solution.

Dilute the reconstituted Provocholine solution:

- Using sterile, empty USP Type 1 borosilicate glass vials, dilute the reconstituted Provocholine solution with 0.9% saline or 0.9% saline with 0.4% phenol either by doubling the concentration (see Table 3) or quadrupling the concentration (see Table 4).
- After adding the diluent shake each vial to obtain a clear solution.
- Use the same diluent to prepare all concentrations.

Use a sterile bacterial-retentive filter (porosity 0.22 µm) when transferring the reconstituted or diluted solution from each vial (at least 2 mL) to a nebulizer.

Refrigerate the reconstituted and diluted solutions at 36° to 46°F (2° to 8°C) for up to 2 weeks. Since the temperature of the solution affects nebulizer output, solutions should be taken out of the refrigerator and allowed to equilibrate to room temperature (approximately 30 minutes) before use.

**Table 3: Reconstitution and Dilution of Supplied Provocholine Powder: Doubling Concentrations**

<b>TAKE</b>	<b>ADD 0.9% Saline or 0.9% Saline with 0.4% Phenol</b>	<b>Concentration (Total volume) after reconstitution or dilution</b>
100 mg of Provocholine Powder in one supplied vial	6.25 mL	16 mg/mL (6.25 mL) (Solution A)
3 mL of Solution A	3 mL	8 mg/mL (6 mL) (Solution B)
3 mL of Solution B	3 mL	4 mg/mL (6 mL) (Solution C)
3 mL of Solution C	3 mL	2 mg/mL (6 mL) (Solution D)
3 mL of Solution D	3 mL	1 mg/mL (6 mL) (Solution E)
3 mL of Solution E	3 mL	0.5 mg/mL (6 mL) (Solution F)
3 mL of Solution F	3 mL	0.25 mg/mL (6 mL) (Solution G)
3 mL of Solution G	3 mL	0.125 mg/mL (6 mL) (Solution H)
3 mL of Solution H	3 mL	0.0625 mg/mL (6 mL) (Solution I)

**Table 4: Reconstitution and Dilution of Supplied Provocholine Powder: Quadrupling Concentrations**

<b>TAKE</b>	<b>ADD 0.9% Saline or 0.9% Saline with 0.4% Phenol</b>	<b>Concentration (Total Volume) after reconstitution or dilution</b>
100 mg of Provocholine Powder in one supplied vial	6.25 mL	16 mg/mL (6.25 mL) (Solution 1)
3 mL of Solution 1	9 mL	4 mg/mL (12 mL) (Solution 2)
3 mL of Solution 2	9 mL	1 mg/mL (12 mL) (Solution 3)
3 mL of Solution 3	9 mL	0.25 mg/mL (12 mL) (Solution 4)
3 mL of Solution 4	9 mL	0.0625 mg/mL (12 mL) (Solution 5)

## 2.6 Calculation and Interpretation of Methacholine Challenge Test Results

A positive methacholine challenge test is a 20% reduction in the FEV<sub>1</sub> (after Provocholine oral inhalation) compared with the mean baseline value (after oral inhalation of the diluent). Calculate and record this value before the methacholine challenge test is started. Express airway hyperreactivity as the provocative Provocholine concentration (mg/mL) providing a fall in FEV<sub>1</sub> of 20% (PC<sub>20</sub>) when the methacholine challenge test is dosed using either the 5-breath dosimeter method or the 2-minute tidal breathing method, or as the provocative Provocholine dose (mcg) providing a fall in FEV<sub>1</sub> of 20% (PD<sub>20</sub>) when using the 2-minute tidal breathing method

### Calculation of PC<sub>20</sub>

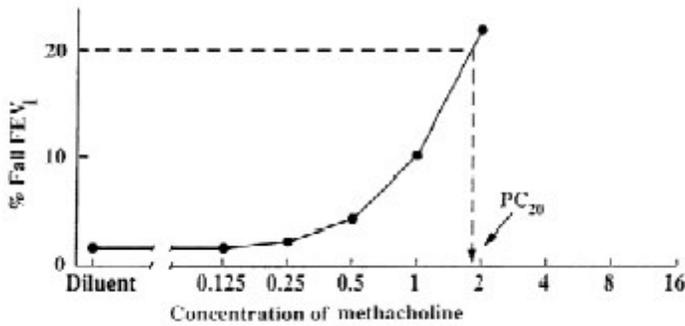
Calculate PC<sub>20</sub> using one of the following methods. Determine the percent decrease in FEV<sub>1</sub> using the mean baseline FEV<sub>1</sub> and the lowest FEV<sub>1</sub> post-dose, as shown below:

$$\% \text{ fall in FEV}_1 = \frac{\text{mean baseline FEV}_1 - \text{lowest FEV}_1 \text{ post-Provocholine}}{\text{mean baseline FEV}_1} \times 100$$

#### *Method #1*

Plot the percent decrease in FEV<sub>1</sub> against the increasing methacholine concentration using a log scale and obtain the PC<sub>20</sub> by linear interpolation between the last two points, as shown in Figure 1.

**Figure 1: Calculation of PC<sub>20</sub>**



*Method #2*

Alternatively, calculate the PC<sub>20</sub> as follows:

$$PC_{20} = \text{antilog} \left[ \text{Log } C_1 + \frac{(\text{Log } C_2 - \text{Log } C_1)(20 - R_1)}{R_2 - R_1} \right]$$

Where:

- C<sub>1</sub> = second last methacholine concentration (<20% FEV<sub>1</sub> decrease)
- C<sub>2</sub> = last methacholine concentration (>20% FEV<sub>1</sub> decrease)
- R<sub>1</sub> = % fall FEV<sub>1</sub> after C<sub>1</sub>
- R<sub>2</sub> = % fall FEV<sub>1</sub> after C<sub>2</sub>

Calculation of PD<sub>20</sub> (2-minute tidal breathing method only)

Calculate the PD<sub>20</sub> as follows:

$$PD_{20} = \text{antilog} \left[ \log D_1 + \frac{[(\log D_2 - \log D_1)(20 - R_1)]}{(R_2 - R_1)} \right]$$

Where:

- D<sub>1</sub> = second last Provocholine dose (<20% FEV<sub>1</sub> decrease)
- D<sub>2</sub> = last Provocholine dose (>20% FEV<sub>1</sub> decrease)
- R<sub>1</sub> = % FEV<sub>1</sub> decrease after D<sub>1</sub>
- R<sub>2</sub> = % FEV<sub>1</sub> decrease after D<sub>2</sub>

When using the English Wright nebulizer, refer to Table 2 for D<sub>1</sub> and D<sub>2</sub>.

Interpretation of Results

A negative (normal) methacholine challenge result is defined as FEV<sub>1</sub> reduction of less than 20% after all the doses (doubling or quadrupling dose increments) in Table 1 (for 5-breath dosimeter method) or Table 2 (for the 2-minute tidal breathing method) have been administered.

If asthma drugs are discontinued prior to the methacholine challenge test consider the possibility of rebound airway hyperreactivity in the interpretation of the test results. The methacholine challenge test

may occasionally be false positive after an influenza infection or upper respiratory infection, immunizations, in very young or very old patients, in patients with chronic lung disease (e.g., cystic fibrosis, sarcoidosis, tuberculosis, chronic obstructive pulmonary disease), in patients with allergic rhinitis without asthma symptoms, in smokers, or in patients after exposure to air pollutants.

### **3 DOSAGE FORMS AND STRENGTHS**

Powder for Solution: 100 mg of white to off-white crystalline powder in amber glass vials (powder is reconstituted and then diluted prior to administration)

### **4 CONTRAINDICATIONS**

Provocholine is contraindicated in the following situations:

- Hypersensitivity to methacholine or other parasympathomimetic agents. Reactions have included rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.
- Baseline FEV<sub>1</sub> <60% predicted (adults or pediatric patients) or <1.5 L (adults)

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Risk of Severe Bronchoconstriction**

Severe bronchoconstriction can result from the Provocholine administration (including the lowest dose). The use of Provocholine is contraindicated in pediatric and adult patients with baseline FEV<sub>1</sub> <60% predicted or adults with FEV<sub>1</sub> <1.5 L. Emergency equipment and medication should be immediately available to treat acute respiratory distress. Because of the potential for severe bronchoconstriction, the use of Provocholine in patients with clinically apparent asthma or wheezing is not recommended. If severe bronchoconstriction occurs, reverse immediately by the administration of a rapid-acting inhaled β-agonist.

If the baseline spirometry is not performed or measured accurately, the initial FEV<sub>1</sub> may be underestimated. In this situation, decreases in FEV<sub>1</sub> may not be detected after escalating Provocholine doses, which may result in administration of unnecessary higher doses and an increase in the risk for excessive bronchoconstriction.

#### **5.2 Risks to Healthcare Providers Administering Provocholine**

The supplied Provocholine powder or the Provocholine aerosol (after reconstitution and/or dilution) may cause bronchoconstriction in healthcare providers administering Provocholine (methacholine challenge test). Healthcare providers and any other personnel involved in administration of Provocholine should take the following precautionary steps:

- Do not inhale the supplied Provocholine powder
- Do not handle the Provocholine powder if you have asthma or hay fever.
- Apply a low resistance filter to expiratory ports of dosing apparatus, as necessary, to prevent Provocholine release in the room air

### 5.3 Coexisting Diseases and Conditions

Provocholine (methacholine challenge test) is not recommended for patients with uncontrolled hypertension, aortic aneurysm, or history of myocardial infarction or stroke diseases. Patients with epilepsy, vagotonia, peptic ulcer disease, thyroid disease, urinary tract obstruction or other condition that could be adversely affected by a cholinergic agent should undergo methacholine challenge only if the healthcare practitioner feels the benefit to the individual outweighs the potential risks.

## 6 ADVERSE REACTIONS

The following adverse reactions associated with the use of Provocholine were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Bronchospasm (includes symptoms such as chest tightness, cough or wheezing).

Adverse reactions less commonly associated with Provocholine were include headache, throat irritation, light-headedness and itching.

## 7 DRUG INTERACTIONS

### Beta-Adrenergic Blockers

The use of beta-adrenergic blockers may impair reversal of Provocholine-caused bronchoconstriction.

### Beta-Agonists, Anticholinergics, and Theophylline

Beta-agonists, anticholinergics, and theophylline inhibit the response of airways to Provocholine; therefore, hold these drugs before Provocholine use for the following duration:

- Short-acting  $\beta$ -agonists (e.g., albuterol): 6 hours
- Long-acting  $\beta$ -agonists (e.g., salmeterol): 36 hours
- Short-acting anti-cholinergics (e.g., ipratropium): 12 hours
- Long-acting anti-cholinergics (e.g., tiotropium):  $\geq 168$  hours
- Oral theophylline: 12-48 hours

### Oral or Inhaled Corticosteroids, and Inhaled Cromoglycate

Regular use of oral or inhaled corticosteroids and inhaled cromoglycate may acutely decrease bronchial responsiveness to Provocholine. However, these drugs may be continued with Provocholine use.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

The available data from published literature on Provocholine use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies evaluating effects of methacholine chloride on embryofetal development have not been conducted. Diagnosis of bronchial airway hyperreactivity with

bronchoprovocation challenge is not recommended for pregnant women because of the potential for hypoxia. If bronchial airway hyperactivity is suspected, consider trial of empiric treatment.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

## 8.2 Lactation

### Risk Summary

There are no available data on the presence of methacholine chloride in human milk, the effect on the breastfed infants, or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Provocholine and any potential adverse effects on the breastfed infant from Provocholine or from the underlying maternal condition.

## 8.4 Pediatric Use

Provocholine is indicated for the diagnosis of bronchial airway hyperreactivity (methacholine challenge test) in pediatric patients 5 years of age and older who do not have clinically apparent asthma. The safety and effectiveness of Provocholine have not been established in pediatric patients below the age of 5 years.

## 8.5 Geriatric Use

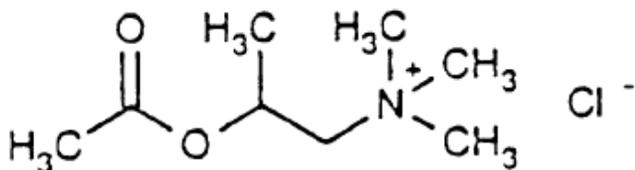
The diagnosis of bronchial airway hyperreactivity is largely performed in pediatric and younger adult patients. Clinical studies of Provocholine did not include patients 65 years of age or older.

## 11 DESCRIPTION

Provocholine (methacholine chloride powder for solution) is a parasympathomimetic (cholinergic) bronchoconstrictor agent to be administered by oral inhalation.

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, alcohol and chloroform and insoluble in ether. Aqueous solutions are neutral to litmus.

Methacholine chloride has an empirical formula of  $C_8H_{18}ClNO_2$ , a molecular weight of 195.69, and the following structural formula:



Each vial of Provocholine contains 100 mg of methacholine chloride powder.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Methacholine chloride is a cholinergic agonist. Bronchial smooth muscle contains significant parasympathetic (cholinergic) innervation. Methacholine chloride agonizes the muscarinic receptors which eventually induce bronchoconstriction.

### **12.2 Pharmacodynamics**

After oral inhalation of Provocholine, patients with asthma are more sensitive to Provocholine-induced bronchoconstriction than are healthy subjects. This difference in response is the pharmacological basis for Provocholine (the methacholine challenge test).

### **12.3 Pharmacokinetics**

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

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 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.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

Provocholine (methacholine chloride powder for solution) is supplied in amber glass vials that contain 100 mg of methacholine chloride powder, white to off-white in color. Cartons have 6 vials (NDC 64281-100-06).

Store the supplied powder at 59° to 86°F (15° to 30°C). Refrigerate the reconstituted and diluted solutions at 36° to 46°F (2° to 8°C) for up to 2 weeks [see *Dosage and Administration (2.5)*].

## **17 PATIENT COUNSELING INFORMATION**

### Risk of Severe Bronchoconstriction

Inform the patient or caregiver that severe bronchoconstriction can result from the Provocholine administration [see *Warnings and Precautions (5.1)*].

### Cough, Chest Tightness, or Shortness of Breath

Inform the patient or caregiver that Provocholine may produce mild cough, chest tightness or shortness of breath.



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