PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrPROVOCHOLINE®

Methacholine Chloride (powder)
USP

100 mg, 160 mg, 320 mg, 1280 mg and 1600 mg

PrPROVOCHOLINE® INHALATION SOLUTION (STERILE)

Methacholine Chloride Inhalation Solution

0 mg / mL, 0.0625 mg / mL, 0.25 mg / mL, 1 mg / mL, 4 mg / mL and 16 mg / mL

Cholinergic/Diagnostic Aid (Bronchial Airway Hyperresponsiveness)

Methapharm Inc.
81 Sinclair Boulevard
Brantford, Ontario
N3S 7X6

Date of Initial Authorization:
<Feb. 25, 1999>

Date of Revision:
< Oct. 28, 2022>

Submission Control No: 249113

RECENT MAJOR LABEL CHANGES

1 Indications	[11/2021]
2 Contraindications	[11/2021]
3 Serious Warnings and Precautions Box	[11/2021]
4 Dosage and Administration	[11/2021]
7 Warnings and Precautions	[11/2021]

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

Provocholine is to be administered only by inhalation. Provocholine is a bronchoconstrictor agent for diagnostic purposes only, and should not be used as a therapeutic agent.

The product should be administered under the supervision of a qualified health professional who is experienced in the use of inhalation agents and in the management of patients experiencing severe bronchoconstriction. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

1.1 Pediatrics

Pediatrics < 5 years of age: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Provocholine for the methacholine challenge test in pediatric patients below the age of 5 years has not been established; therefore, Health Canada has not authorized an indication for pediatric use < 5 years of age.

1.2 Geriatrics

Geriatrics: No data are available to Health Canada in patients 65 years of age or older; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

- Provocholine (methacholine chloride) is contraindicated in patients who are hypersensitive to this drug or other parasympathomimetic agents, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING [6].
- A repeat challenge test on the same day is contraindicated
- β-agonists, anticholinergics and theophylline may be contraindicated (See DRUG INTERACTIONS [9])
- The use of Provocholine is contraindicated in pediatric and adult patients with baseline FEV_1 <70% predicted or adults with FEV_1 <1.5 L

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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_1 <70% predicted or adults with FEV_1 <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 (7)].

- 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 (β-agonist) [see Warnings and Precautions (7)].

- If baseline spirometry is not performed or measured inaccurately, the initial FEV_1 may be underestimated. In this situation, decreases in FEV_1 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 (7)]

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Use of Provocholine is not recommended in patients with clinically apparent asthma or wheezing. 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 supervised withdrawal of asthma drugs.

- Provocholine should be administered in a methacholine challenge test 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 the methacholine challenge test and the management of respiratory distress.

- Before starting a methacholine challenge test, baseline spirometry must be performed. For a patient to be able to undergo the test, he or she must present with baseline FEV_1 (Forced Expiratory Volume in 1 second) greater than or equal to 70% of the predicted value (in adults and children) and greater than or equal to 1.5 L (in adults).

At commencement of the methacholine challenge test and prior to nebulization with Provocholine, FEV_1 must be measured following exposure to nebulized diluent to obtain the post-diluent FEV_1 using the following solutions:

- 0.9% sodium chloride (saline) or 0.9% sodium chloride with 0.4% phenol (0.9% saline with 0.4% phenol) or 0.9% sodium chloride with 0.9% benzyl alcohol (0.9% saline with 0.9% benzyl) when using Provocholine powder. Use the same diluent that is used to reconstitute the Provocholine powder.
- 0 mg / mL solution when using Provocholine Inhalation Solution

The methacholine challenge test is considered positive if there is a reduction in FEV_1 of 20% or more from post-diluent FEV_1. The test should be stopped at this point. The reduction value must be calculated and recorded before starting the test with Provocholine.

- For the methacholine challenge test, use either Provocholine powder to prepare the methacholine chloride concentrations / doses or use the Provocholine Inhalation Solution (See Recommended Dose and Dosage Adjustment [4.2]).

- The methacholine challenge test is performed by giving a subject increasing serial concentrations of Provocholine (Recommended Dose and Dosage Adjustment [4.2]). Administer Provocholine concentrations / doses by oral inhalation using either the 5-Breath Dosimeter Dosing Method or the 2-Minute Tidal Breathing Dosing method (Administration [4.4]).

- An inhaled β-agonist must be administered after a methacholine challenge test with Provocholine to expedite the return of the FEV_1 to baseline and to relieve any discomfort of the subject. Most patients revert to normal pulmonary function within 10 to 20 minutes following administration of a β-agonist.

4.2 Recommended Dose and Dosage Adjustment

For the methacholine challenge test using Provocholine powder (methacholine chloride USP), adults and children (5 years or older) are exposed to increasing concentrations of nebulized methacholine chloride solutions using either doubling dosing or quadrupling dosing. Provocholine powder requires reconstitution and dilution before use. See Section 4.3.1 Preparation of Provocholine Powder Solutions.

For the methacholine challenge test using Provocholine Inhalation Solution adults and children (5 years or older) are exposed to increasing concentrations of nebulized methacholine chloride solutions (quadrupling dosing). The 0 mg / mL solution is used to obtain baseline spirometry (FEV_1).

Quadrupling Dosing:
0.0625, 0.25, 1, 4, and 16 mg / mL.

Doubling Dosing:
0.03125, 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 mg / mL.

4.3 Reconstitution

4.3.1 Preparation of Provocholine Powder Solutions

Provocholine powder (methacholine chloride USP) requires reconstitution and dilution before use. Refer to specific instructions below for reconstitution and dilution of either 100 mg, 160 mg, 320 mg, 1280 mg or 1600 mg vial of Provocholine powder. All dilutions using Provocholine powder should be made with 0.9% sodium chloride solution for injection (saline) or 0.9% sodium chloride solution with 0.4% phenol (saline with 0.4% phenol) or 0.9% sodium chloride solution for injection with 0.9% benzyl alcohol (saline with 0.9% benzyl).

Use sterile USP Type I glass vials for the dilution preparations. After adding the 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl, shake each vial to obtain a clear solution. Check the date of preparation or expiry before using dilutions that are not freshly prepared. **(Note: When preparing dilutions, use only the same kind of diluent to prepare all concentrations).**

When preparing dilutions using Provocholine powder, a sterile bacterial retentive filter (porosity 0.22 mcm) should be used when transferring a solution from each vial (at least 2 mL) to a nebulizer.

Reconstitution and Dilution of Provocholine Solutions using 100 mg vial of Provocholine Powder

Refer to Table 1 for the preparation of the solutions for the doubling dosing using the 100 mg vial of Provocholine powder.

Table 1: Preparation of Doubling Dose Serial Dilutions Using a Single 100 mg Vial of Provocholine Powder (methacholine chloride USP) (for both 20 mL and 50 mL vial sizes)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
100 mg Provocholine	6.25 mL	16 mg / mL (A)
3 mL of dilution A	3 mL	8 mg / mL (B)
3 mL of dilution B	3 mL	4 mg / mL (C)
3 mL of dilution C	3 mL	2 mg / mL (D)
3 mL of dilution D	3 mL	1 mg / mL (E)
3 mL of dilution E	3 mL	0.5 mg / mL (F)
3 mL of dilution F	3 mL	0.25 mg / mL (G)
3 mL of dilution G	3 mL	0.125 mg / mL (H)
3 mL of dilution H	3 mL	0.0625 mg / mL (I)
3 mL of dilution I	3 mL	0.03125 mg / mL (J)

Refer to Table 2 for the preparation of the solutions for the quadrupling dosing using the 100 mg vial of Provocholine powder.

Table 2: Preparation of Quadrupling Dose Serial Dilutions Using a Single 100 mg Vial of Provocholine Powder (methacholine chloride USP) (for both 20 mL and 50 mL vial sizes)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
100 mg Provocholine	6.25 mL	16 mg / mL (A)
3 mL of dilution A	9 mL	4 mg / mL (B)
3 mL of dilution B	9 mL	1 mg / mL (C)
3 mL of dilution C	9 mL	0.25 mg / mL (D)
3 mL of dilution D	9 mL	0.0625 mg / mL (E)

Reconstitution and Dilution of Provocholine Solutions using 160 mg or 320 mg vials of Provocholine powder

Refer to Tables 3 and 4, respectively, for the reconstitution of the 160 mg and 320 mg vials of Provocholine powder to obtain a solution of 16 mg / mL concentration of Provocholine. This 16 mg / mL solution can be used to prepare dilutions to obtain the doubling or quadrupling doses as shown in Tables 1 and 2, respectively.

Table 3: Reconstitution of a Single 160 mg Vial of Provocholine Powder (methacholine chloride USP)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
160 mg Provocholine	10 mL	16 mg / mL

Table 4: Reconstitution of a Single 320 mg Vial of Provocholine Powder (methacholine chloride USP)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
320 mg Provocholine	20 mL	16 mg / mL

Reconstitution and Dilution of Provocholine Solutions using 1280 mg or 1600 mg Vials of Provocholine Powder

Refer to Tables 5 and 6, respectively, for the reconstitution and dilution of the 1280 mg and 1600 mg vials of Provocholine powder to obtain a solution of 16 mg / mL concentration of Provocholine. For the remaining dilutions using the 16 mg / mL solution to obtain either doubling or quadrupling dose solutions, prepare as shown in Tables 1 and 2 respectively.

NOTE: The initial dilutions of the 1280 mg and 1600 mg vials to obtain solutions of 128 mg / mL (1280 mg) and 32 mg / mL (1600 mg) or are NOT to be administered to the patient during the methacholine challenge test with Provocholine. They are only used in the preparation of the 16 mg / mL dilutions.

Table 5: Reconstitution of a Single 1280 mg Vial of Provocholine Powder (methacholine chloride USP)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
1280 mg Provocholine	10 mL	128 mg / mL (X)
1 mL of dilution X	7 mL	16 mg / mL

Table 6: Preparation of Doubling Dose Serial Dilutions Using a Single 1600 mg Vial of Provocholine Powder (methacholine chloride USP)

TAKE	ADD 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl	OBTAIN DILUTION
1600 mg Provocholine	50 mL	32 mg / mL (Y)
3 mL of dilution Y	3 mL	16 mg / mL

4.3.2 Using Provocholine Inhalation Solution

The Provocholine Inhalation Solution provides for the quadrupling doses in the methacholine chloride concentrations 0.0625, 0.25, 1, 4, and 16 mg / mL. These solutions do not require dilution before use.

4.4 Administration

Two methods of administration of the methacholine challenge test with Provocholine have been widely used in current clinical practice; the tidal breathing method and the dosimeter method. The tidal breathing technique requires the patient to breathe normally, over a two-minute period, an aerosol of Provocholine. By contrast, the dosimeter method requires the patient to take five full breaths of Provocholine aerosol generated by an appropriate dosimeter. Approved manufacturer's instructions should be followed when using these devices. The test is stopped if

the FEV_1 falls by 20% or more from the post-diluent FEV_1. The concentration and the percent fall in FEV_1 are then used to calculate the provocative concentration to cause a fall in FEV_1 of 20% (PC_{20}).

4.4.1 Two (2)-Minute Tidal Breathing Method

The following method is based on the use of the English Wright nebulizer. Ensure device output and particle size are characterized for the nebulizer being used.

Prior to administering the Provocholine dose (s), determine the post-diluent FEV_1 required for the methacholine challenge test as follows:

- When using Provocholine solutions prepared from Provocholine powder, administer the same diluent used to reconstitute the Provocholine powder.
- When using Provocholine Inhalation Solution, administer the 0 mg / mL solution.

Administration of the Diluent to Obtain Post-Diluent FEV_1 Value

1. When using Provocholine Powder:

   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 or 0.9% saline with 0.9% benzyl). Dispense into the nebulizer using a sterile bacterial-retentive filter (porosity 0.22 mcm).

   When using Provocholine Inhalation Solution:

   Dispense the contents of a vial containing the 0 mg / mL solution into the nebulizer.

2. Instruct the patient to relax and breathe the aerosol quietly (tidal breathing) for 2 minutes of inhalation time.
3. Place the mouthpiece in the mouth (with a nose clip) or a face mask loosely over the nose and mouth of the patient. The patient should hold the nebulizer to avoid warming the solution. The nebulizer should be kept upright and vertical.
4. Start the nebulizer by adjusting the flow meter so that the nebulizer is operating at the calibrated output (0.13 mL / minute for the English Wright nebulizer). Start the stopwatch immediately.
5. After exactly 2 minutes, turn off the flow meter, remove the mouthpiece from the mouth (or the face mask), and discard any remaining solution.
6. Perform spirometry and measure the FEV_1 30 and 90 seconds after the end of the inhalation to obtain the post-diluent FEV_1. These values may be left at ambient (spirometer) temperature pressure saturated (ATPS). If the FEV_1 value is not of acceptable quality, repeat the procedure. If the post-diluent FEV_1 falls by ≥ 20% from baseline FEV_1, do not give further inhalations and proceed to Step 9. If the post-diluent FEV_1 falls by < 20% from baseline FEV_1, continue to Step 7.

Administration of Provocholine in a Methacholine Challenge Test

7. When using Provocholine Powder:

   Using a 3 mL syringe and needle, draw up the appropriate Provocholine concentration starting with the lowest dose and dispense into the nebulizer using a sterile bacterial-retentive filter (porosity 0.22 mcm). See Table 1 for preparation of the Provocholine solution per the doubling dose method and Table 2 for preparation of the Provocholine solution per the quadrupling dose method.

   When using Provocholine Inhalation Solution:

   Dispense the contents of a vial of the appropriate Provocholine concentration, starting with the lowest dose, into the nebulizer. The Provocholine solution concentrations, 0.0625, 0.25, 1, 4, and 16 mg / mL, provided in the carton do not require dilution before use.

8. Repeat steps 2 through 6 for each Provocholine dose, emptying the nebulizer between each dose. To keep the cumulative effect of Provocholine relatively constant, the time interval between commencement of two subsequent concentrations should be kept to 5 minutes. However, stop dosing if the FEV_1 has fallen by ≥ 20% from the post-diluent FEV_1 or the highest Provocholine concentration (16 mg / mL) has been administered (whichever comes first). For severe bronchoconstriction, see Warnings and Precautions [7]. Do not administer additional Provocholine doses.

9. After the test is completed, administer an inhaled β-agonist to the patient to expedite the return of the FEV_1 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 β-agonist administration). Wait 10 minutes and measure the FEV_1 and Vital Capacity. Patients should not be allowed to leave the laboratory until their FEV_1 has returned to within 90% of baseline.

10. After the test, wash and clean reusable nebulizers thoroughly according to manufacturer's recommendations and discard disposable nebulizers appropriately.

4.4.2 Five (5)-Breath Dosimeter Dosing Method

The following method is based on the use of a five-breath dosimeter.

Prior to administering the Provocholine dose(s), determine the post-diluent FEV_1 required for the methacholine challenge test as follows:

- When using Provocholine solutions prepared from Provocholine powder, administer the same diluent used to reconstitute the Provocholine powder.
- When using Provocholine Inhalation Solution, administer the 0 mg / mL solution.

Administration of the Diluent or 0 mg / mL Solution to Obtain Post-Diluent FEV_1 Value

1. When using Provocholine Powder:

   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 or 0.9% saline with 0.9% benzyl). Dispense into the nebulizer using a sterile bacterial-retentive filter (porosity 0.22 mcm).

   When using Provocholine Inhalation Solution:

   Dispense the contents of a vial containing the 0 mg / mL solution into the nebulizer.

2. Instruct the patient to hold the nebulizer upright with the mouthpiece in his / her mouth. The patient should wear a nose clip while inhaling from the nebulizer.

3. At the end of 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_1 30 and 90 seconds after the fifth inhalation from the nebulizer to obtain the post-diluent FEV_1 value. These values may be left at ambient (spirometer) temperature pressure saturated (ATPS). If the FEV_1 value is not of acceptable quality, repeat the procedure. If the post-diluent FEV_1 falls by ≥ 20% from baseline FEV_1, do not give further inhalations and proceed to Step 8. If the post-diluent FEV_1 falls by < 20% from baseline FEV_1, continue to Step 6.

Administration of Provocholine in a Methacholine Challenge Test

6. When using Provocholine Powder:

   Using a 3 mL syringe and needle, draw up the appropriate Provocholine concentration starting with the lowest dose and dispense into the nebulizer using a sterile bacterial-retentive filter (porosity 0.22 mcm). See Table 1 for preparation of the Provocholine solution per the doubling dose method and Table 2 for preparation of the Provocholine solution per the quadrupling dose method.

   When using Provocholine Inhalation Solution :

   Dispense the contents of a vial of the appropriate Provocholine concentration, starting with the lowest dose, into the nebulizer. The Provocholine Inhalation Solution concentrations, 0.0625, 0.25, 1, 4, and 16 mg / mL, provided in the carton do not require dilution before use.

7. Repeat steps 2 through 5 for each Provocholine concentration, emptying the nebulizer between each concentration. 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.

8. Stop dosing if the FEV_1 has fallen by ≥ 20% from the post-diluent FEV_1, or the highest Provocholine concentration (16 mg / mL) has been administered (whichever comes first). For severe bronchoconstriction, see Warnings and Precautions [7]. Do not administer additional Provocholine concentrations.

9. After the test is completed, administer an inhaled β-agonist to the patient to expedite the return of the FEV_1 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 β-agonist administration). Wait 10 minutes and measure the FEV_1 and Vital Capacity. Patients should not be allowed to leave the laboratory until their FEV_1 has returned to within 90% of baseline.

10. After the test, wash and clean reusable nebulizers thoroughly according to manufacturer's recommendations.

Calculation and Interpretation of Results:

The provocative concentration (PC_{20}) or the provocative dose (PD_{20}) causing a 20% fall in FEV_1 may be calculated as described below:

1. Calculation of PC_{20}

With either the tidal breathing method or the dosimeter method, airway responsiveness may be expressed as that concentration of Provocholine provoking a fall in FEV_1 of ≥ 20% (PC_{20}). The percent fall in FEV_1 can be calculated using the post-diluent FEV_1, as shown below:

$$\% \text{ fall in } FEV_1 = \frac{\text{post-diluent } FEV_1 - \text{lowest } FEV_1 \text{ post-Provocholine}}{\text{post-diluent } FEV_1} \times 100$$

The percent fall in is then plotted against the rising concentration of Provocholine (log scale). The PC_{20} is obtained by linear interpolation between the last two points, as shown in Figure 1.

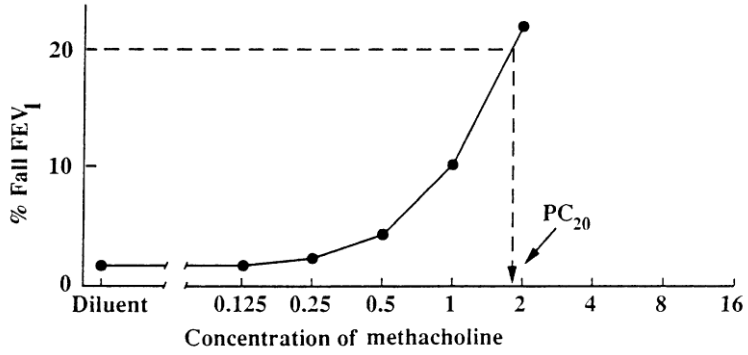


Figure 1: Calculation of PC_{20}

Alternatively, the PC_{20} may be calculated as follows:

$$PC_{20} = \text{antilog}\left[\log C1 + \frac{(\log C2 - \log C1)(20 - R1)}{(R2 - R1)}\right]$$

Where:
C1 = second last concentration (<20% FEV_1 fall)
C2 = last concentration (>20% FEV_1 fall)
R1 = % fall FEV_1 after C1
R2 = % fall FEV_1 after C2

2. Calculation of PD_{20}

The PD_{20} may be calculated as follows:

$$PD_{20} = \text{antilog}\left[\log D1 + \frac{(\log D2 - \log D1)(20 - R1)}{(R2 - R1)}\right]$$

Where:
D1 = second last dose (<20% FEV_1 fall)
D2 = last dose (>20% FEV_1 fall)
R1 = % fall FEV_1 after D1
R2 = % fall FEV_1 after D2

Substituting nebuliser devices with different characteristics (output rate and particle size distribution) would be expected to deliver a different Provocholine dose at the same solution concentration. In the case of substitution of the nebuliser device and to improve test standardisation, it will be important to report aerosol amount/airway responsiveness to Provocholine in terms of dose/PD_{20} and not concentration/PC_{20}. Knowledge of the device relating to device output per minute, the particle size distribution, time of tidal breathing and ratio of inspiratory time to total breathing time will enable the calculation of the dose.

3. Interpretation of Results

A negative (normal) methacholine challenge result is defined as FEV_1 reduction of < 20% after all the doses (doubling or quadrupling dose increments) up to 16 mg / mL have been administered.

If asthma drugs are discontinued prior to the methacholine challenge test, consider the possibility of rebound airway hyperresponsiveness in the interpretation of the test results. The methacholine challenge test may occasionally be falsely 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.

5 OVERDOSAGE

Provocholine (methacholine chloride) is to be administered only by inhalation. When administered orally or by injection, overdosage with Provocholine 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 intramuscular or intravenous.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 9 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Inhalation	Powder 100 mg, 160 mg, 320 mg, 1280 mg and 1600 mg	No excipients.
Inhalation	Solution 0.0625 mg / mL, 0.25 mg / mL,1 mg / mL, 4 mg / mL, 16 mg / mL The 0 mg / mL solution contains no methacholine chloride	sodium acetate trihydrate, sodium chloride, glacial acetic acid as pH adjuster

Provocholine Powder:

- 100 mg – in 20 mL amber glass vials in cartons of 6
- 100 mg – in 50 mL amber glass vials
- 160 mg – in 20 mL amber glass vials
- 320 mg – in 20 mL amber glass vials
- 1280 mg – in 20 mL amber glass vials in cartons of 6
- 1600 mg – in 50 mL amber glass vials

Provocholine Inhalation Solution (Sterile):
Each carton has six plastic vials with twist-off cap each containing 3 mL of the following concentrations of methacholine chloride:

Strength	Total Content per Vial
0 mg / mL	0 mg / 3 mL
0.0625 mg / mL	0.1875 mg / 3 mL
0.25 mg / mL	0.75 mg / 3 mL
1 mg / mL	3 mg / 3 mL
4 mg / mL	12 mg /3 mL
16 mg / mL	48 mg / 3 mL

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

Provocholine (methacholine chloride) is to be administered only by inhalation. Provocholine is a bronchoconstrictor agent for diagnostic purposes only, and should not be used as a therapeutic agent.

Administration of Provocholine 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 the benefit to the individual outweighs the potential risks.

It is essential that the baseline spirometry is accurate. If the baseline spirometry is not performed or measured accurately, and the initial FEV_1 is underestimated, subsequent falls after inhaling Provocholine solutions may not be detected, resulting in too high a dose and excessive bronchoconstriction.

Methacholine challenge test with Provocholine 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. A physician responsible for the tests must be present in the building when tests are carried out, and available to be contacted quickly if necessary. If the physician is performing the test, another person must be available in the building to give assistance if required. The patient must never be left unattended during the test.

Emergency medication and equipment should be immediately available to treat acute respiratory distress.

Carcinogenesis and Mutagenesis

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.

Cardiovascular

Administration of Provocholine to patients with cardiovascular disease accompanied by bradycardia, which could be adversely affected by a cholinergic agent, should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

Endocrine and Metabolism

Administration of Provocholine to patients with thyroid disease, which could be adversely affected by a cholinergic agent, should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

Gastrointestinal

Administration of Provocholine to patients with peptic ulcer disease, which could be adversely affected by a cholinergic agent, should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

Genitourinary

Administration of Provocholine to patients with urinary tract obstruction, which could be adversely affected by a cholinergic agent, should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

Neurologic

Administration of Provocholine to patients with epilepsy, which could be adversely affected by a cholinergic agent, should be undertaken only if the physician feels benefit to the individual outweighs the potential risks.

Respiratory

Severe bronchoconstriction can result from the administration of Provocholine, if guidelines for careful administration are not followed. The use of Provocholine is contraindicated in pediatric and adult patients with baseline FEV_1 <70% predicted or adults with FEV_1 <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.

Patients with severe hyperresponsiveness of the airways can experience bronchoconstriction at the lowest dosages of Provocholine, or with the diluent (or placebo, as applicable) alone. Emergency equipment and medication should be immediately available to treat acute respiratory distress. If severe bronchoconstriction occurs, it should be reversed immediately by the administration of a rapid acting inhaled bronchodilator agent (ß agonist).

If baseline spirometry is not performed or measured inaccurately, the initial FEV_1 may be underestimated. In this situation, decreases in FEV_1 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.

Fertility

There have been no studies with methacholine chloride that would permit an evaluation of its effect on fertility.

7.1 Special Populations

7.1.1 Pregnant Women

Teratogenic Effects - 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. Provocholine should be given to a pregnant woman only when the benefits clearly outweigh the risks.

7.1.2 Breast-feeding

It is not known if methacholine chloride when inhaled is excreted in breast milk. Methacholine challenge test with Provocholine should be administered to nursing mothers only when the benefits clearly outweigh the risks.

7.1.3 Pediatrics

The safety and efficacy of methacholine challenge tests with Provocholine have not been established in children below the age of 5 years.

7.1.4 Geriatrics

The safety and efficacy of methacholine challenge tests with Provocholine have not been established in the geriatric population (≥ 65 years).

8 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 symptoms such as chest tightness, cough or wheezing.

Rare adverse reactions associated with inhaled methacholine chloride used in methacholine challenge tests include incidences of headache, throat irritation, light-headedness and itching.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Provocholine is a parasympathomimetic (cholinergic) bronchoconstrictor agent to be administered in solution only, by inhalation. Methacholine chloride is the β methyl homolog of acetylcholine, is slowly hydrolysed by acetylcholinesterase and almost totally resistant to inactivation by non-specific cholinesterase or pseudocholinesterase.

9.4 Drug-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 β-agonists (e.g., salbutamol): 6 hours
- Long-acting β-agonists (e.g., salmeterol): 36 hours
- Short-acting anti-cholinergics (e.g., ipratropium): 12 hours
- Long-acting anti-cholinergics (e.g., tiotropium): ≥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.

9.5 Drug-Food Interactions

Provocholine can be administered without regards to timing of meals.

9.6 Drug-Herb Interactions

The interactions of methacholine chloride with herbal medications or supplements have not been established.

9.7 Drug-Laboratory Test Interactions

The interactions of Provocholine with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Provocholine (methacholine chloride) is a parasympathomimetic (cholinergic) bronchoconstrictor agent to be administered in solution only, by inhalation, for diagnostic purposes.

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 hydrolysed by acetylcholinesterase and is almost totally resistant to inactivation by non-specific cholinesterase or pseudocholinesterase.

10.2 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 in the methacholine challenge test.

Certain drugs can affect the pharmacodynamic response to Provocholine (See Drug-Drug Interactions [9.4])

10.3 Pharmacokinetics

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

11 STORAGE, STABILITY AND DISPOSAL

Temperature:

- Store unopened vials of Provocholine powder at room temperature (between 15 to 30°C).

- Store Provocholine Inhalation Solution between 15 to 25°C. Protect from light. Use immediately upon opening the vial.

Reconstituted Solutions:

- Provocholine powder reconstituted with 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl, using aseptic technique, may be stored under refrigeration (2° to 8°C) for up to 2 weeks.

12 SPECIAL HANDLING INSTRUCTIONS

Provocholine is a potent bronchoconstrictor. Do not inhale the powder. Do not handle this material if you have asthma or hay fever. A low resistance filter should be applied to an expiratory port of any dosing apparatus, as necessary, to prevent Provocholine aerosol from being released into the air of the room.

PART II: SCIENTIFIC INFORMATION

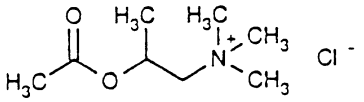
13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Methacholine Chloride USP

Chemical name: 1 Propanaminium, 2 (acetyloxy) N,N,N trimethyl , chloride

Molecular formula and molecular mass: $C_8H_{18}ClNO_2$ and 195.69

Structural formula: 

Physicochemical properties: Methacholine Chloride USP is a white to practically white deliquescent compound that is soluble in water, alcohol and chloroform and insoluble in ether. Aqueous solutions are neutral to litmus.

Product Characteristics

Provocholine powder in vials of either 100 mg, 160 mg, 320 mg, 1280 mg and 1600 mg methacholine chloride must be reconstituted and diluted with either 0.9% saline or 0.9% saline with 0.4% phenol or 0.9% saline with 0.9% benzyl. The solutions are administered via inhalation using a nebulizer.

Provocholine Inhalation Solution contains methacholine chloride solutions in concentrations of 0.0625 mg / mL, 0.25 mg / mL, 1 mg / mL, 4 mg / mL and 16 mg / mL (0 mg / mL solution with no methacholine chloride is also provided). The solutions are ready for administration via inhalation using a nebulizer.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Diagnosis of Bronchial Airway Hyperresponsiveness

Summary of patient demographics for clinical trials in Diagnosis of Bronchial Airway Hyperresponsiveness

In 1,500 patients with asthma and 500 non-asthmatics (either atopic or nonatopic), over 90% of asthmatics had high- or medium-positive responsiveness to methacholine chloride. Less than 5% of individuals with hay fever or nonatopic normal subjects showed a high-positive response. Twenty-seven percent of hay fever patients had a negative response compared to 49% of normal subjects. Hay fever patients and normal subjects had about the same incidence of low-positive responses. Thirty percent of hay fever patients had a medium-positive response compared to 18% of normal subjects from families with a history of asthma and 8% of normal

subjects from control families. Asthmatics were different from all other groups. Hay fever patients were different from normal subjects of normal families only.

Among current asthmatics, the severity of asthma determined the bronchial sensitivity of subjects to methacholine challenge. This sensitivity varied from 100 to several thousand times that of normal subjects. However, in former asthmatics, the degree of bronchoconstriction was also related to the severity of past asthma symptoms. The mean sensitivity of former asthmatics was approximately one-tenth that of current asthmatics.

Population studies in patients with asthma and in non-asthmatics (atopic and non-atopic).

In population-based studies, the prevalence of methacholine chloride hyperresponsiveness is 8 to 15%. While the degree of responsiveness of asthmatics does not distinguish them from non-asthmatics, asthmatics respond to a lower mean dose. Asthmatics that are less responsive generally have milder and more stable disease. Interpretation is easiest when the result is either substantially positive (a PC_{20} <1 mg / mL or a PD_{20} < 0.13 µmoles), or decidedly negative (minimal change in the FEV_1 with the highest dose delivered). The cut-off point between normal and increased responsiveness is considered to be a PC_{20} of 4-16 mg / mL (when using the English Wright 2-min tidal protocol) or a PD_{20} of 0.5-2 µmoles.

Results of studies in Diagnosis of Bronchial Airway Hyperresponsiveness

A dosimeter technique was used to test 766 children aged 9 years, who showed symptoms of asthma but had normal resting pulmonary function. Within two months, the dosimeter method was used to retest 79 of these patients. A further 30, 22 of whom showed reactivity, were challenged with the tidal breathing method. Twenty-five percent of the children had evidence of airway reactivity, revealed either by resting airflow obstruction relieved by salbutamol or by responsiveness to inhalation of methacholine chloride. The dosimeter method was suitably repeatable, and the tidal breathing method was equally sensitive in detecting reactivity to methacholine chloride. In only four children was the difference in PC_{20} between the two techniques greater than a two-fold concentration step. A paired t test showed no bias from one method to the other.

The usefulness of the methacholine challenge test with Provocholine in confirming suspected asthma was determined in 1,105 subjects of 5 to 80 years of age; 189 were current asthmatics and 916 were non-asthmatics. Non-asthmatics were further categorized as: 143 atopics from asthma families; 66 atopics from normal families; 326 nonatopics from asthma families; and 381 nonatopics from normal families. Subjects were challenged with methacholine chloride, using the dosimeter method. Methacholine chloride challenge was shown to be a helpful tool in affirming the pretest probability of asthma.

15 MICROBIOLOGY

No microbiological information is required for this drug product

16 NON-CLINICAL TOXICOLOGY

The acute (24-hour) oral LD_{50} 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrPROVOCHOLINE®
Methacholine Chloride (Powder)

PrPROVOCHOLINE® INHALATION SOLUTION
Methacholine Chloride Inhalation Solution

Read this carefully before you start taking **Provocholine**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Provocholine**.

Serious Warnings and Precautions

- Severe tightening of the airways can occur after using Provocholine. Use of Provocholine is not recommended in patients with asthma or wheezing.
- Provocholine can cause "acute respiratory distress" (severe breathing problems). If this happens after you use Provocholine, your healthcare professional will have emergency equipment and medication on hand to help you.

What is Provocholine used for?
Provocholine is used as a series of breathing tests to diagnose a condition called "bronchial airway hyperresponsiveness" (a sensitivity where your airway narrows). It is used in adults and children 5 years of age and older who do not have asthma. Provocholine is for inhalation only and is always given to you by a healthcare professional.

How does Provocholine work?
Provocholine can cause muscles in the airways to tighten. When a Provocholine mist is inhaled, people with asthma are much more likely to react to it than people without asthma, which helps your doctor measure your lung function.

What are the ingredients in Provocholine?
Medicinal ingredient: Methacholine Chloride
Non-medicinal ingredients (Provocholine): There are no non-medicinal ingredients.
Non medicinal ingredients (Provocholine Inhalation Solution): sodium chloride, sodium acetate trihydrate and glacial acetic acid.

Provocholine comes in the following dosage forms:
Powder (requires reconstitution and dilution prior to use): 100 mg, 160 mg, 320 mg, 1280 mg and 1600 mg.
Solution (does not require dilution before use): 0.0625 mg / mL, 0.25 mg / mL, 1 mg / mL, 4 mg / mL and 16 mg / mL (the 0 mg / mL solution contains no methacholine chloride).

Do not use Provocholine if:

- You are allergic to methacholine chloride or to any of the ingredients in Provocholine (**see What are the ingredients in Provocholine?**).
- You are allergic to other parasympathomimetic agents
- You have already done a 'methacholine challenge test' with Provocholine on the same day - you should not have more than one test on the same day.

- You are taking medicines that are β-agonists or anticholinergics
- You are taking theophylline
- Your lung function test results are low prior to starting a test with Provocholine. In this case, your healthcare professional may decide not to proceed with the test and will contact the doctor who ordered the test.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Provocholine. Talk about any health conditions or problems you may have, including if you:
- have epilepsy.
- have ulcers in the lining of your stomach (peptic ulcer disease).
- have thyroid disease.
- have an obstructed urinary tract.
- have any type of heart disease with a slow heart rate.
- have an irritable vagus nerve (vagotonia).
- are pregnant, think you may be pregnant or are planning to become pregnant.
- are breastfeeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Provocholine:
- Drugs used to treat high blood pressure, called beta-adrenergic blockers.
- Drugs used to relax and open airways (salbutamol, salmeterol), called beta-agonists.
- Drugs called anticholinergics (ipratropium, tiotropium).
- Theophylline, a medication used to treat lung diseases such as asthma.
- Oral or inhaled corticosteroids, used to treat inflammation and swelling.
- Inhaled cromoglycate, a medication used to treat asthma.

How to take Provocholine:
- Provocholine is given to you by a healthcare professional who is experienced in the administration of the methacholine challenge test.
- Provocholine is always given as a solution, by inhalation.

Usual dose:
Your healthcare professional will expose you to increasing concentrations of methacholine chloride solution mist to test your lung function.

The test is done using one of two types of dosing:
- Doubling dosing (0.03125, 0.0625, 0.125, 0.25, 0.5, 1,2,4,8,16 mg / mL) or
- Quadrupling dosing (0.0625, 0.25, 1, 4, 16 mg / mL).

Your healthcare professional will stop the test if:
- Your lung function drops to the target level.
- You have reached the highest dose of Provocholine and your lung function has not dropped to the target level.
- It is determined that you are unable to continue with the test due to symptoms.

At the end of the test, you may be given a reversal agent. Your healthcare professional will

measure your lung function to make sure your breathing is back to normal before you are sent home.

Overdose:

If you think you, or a person you are caring for, have been given too much Provocholine, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Provocholine?

These are not all the possible side effects you may have when taking Provocholine. If you experience any side effects not listed here, tell your healthcare professional.

- Chest tightness
- Cough
- Wheezing
- Throat irritation
- Headache
- Light-headedness
- Itching

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Provocholine is stored by a healthcare professional. It should never be removed from the clinic or lab.

If you want more information about Provocholine:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling 1-866-701-4636 for medical

information inquiries and adverse events, or 1-800-287-7686 for customer service.

This leaflet was prepared by Methapharm Inc.

Last Revised: < Oct. 28, 2022 >