PROVOCHOLINE®

NAME OF THE MEDICINAL PRODUCT
Provocholine

QUALITATIVE AND QUANTITATIVE COMPOSITION
Methacholine chloride powder 100 mg / vial

PHARMACEUTICAL FORM
Powder for solution for inhalation

THERAPEUTIC CLASSIFICATION
Cholinergic / Diagnostic Aid (Bronchial Asthma)

FOR INHALATION ONLY

Serious Warnings and Precautions

- Provocholine is to be administered only by inhalation. **See Warnings and Precautions – General**
- Provocholine is a bronchoconstrictor agent for diagnostic purposes only, and should not be used as a therapeutic agent. **See WARNINGS AND PRECAUTIONS – General**
- Patients with severe hyperesponsiveness of airways can experience bronchoconstriction at the lowest dosages or with the diluent alone. **See WARNINGS AND PRECAUTIONS - Respiratory**
- Test should not be performed on any patient with baseline FEV_1 of less than 1.5 litres or 70% of predicted value. **SEE WARNINGS AND PRECAUTIONS - Respiratory**
- When administered orally or by injection Provocholine is associated with nausea, vomiting, substernal pain or pressure, hypotension, fainting and transient complete heart block. **See ADVERSE REACTIONS**
- When administered orally or by injection overdosage can result in a syncopal reaction, with cardiac arrest and loss of consciousness. **See OVERDOSAGE**
- Baseline spirometry must be accurate. If not, the initial FEV_1 may be underestimated, and subsequent falls after inhaling Provocholine solutions may not be detected, resulting in too high a dose and excessive bronchoconstriction. **See WARNINGS AND PRECAUTIONS - General**

INDICATIONS AND CLINICAL USE

Provocholine (methacholine chloride powder) is indicated for the diagnosis of bronchial airway hyperactivity in subjects who do not have clinically apparent asthma.

CONTRAINDICATIONS

Provocholine is contraindicated in patients with known hypersensitivity to the active substance, to any of the excipients listed in section STORAGE AND STABILITY or to other parasympathomimetic agents.

- A repeat challenge test on the same day is contraindicated.
- β-agonists, anticholinergics and theophylline may be contraindicative (See DRUG INTERACTIONS)

WARNINGS AND PRECAUTIONS

General

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.

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.

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, Mutagenesis and 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.

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.

Neurological

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. Patients with severe hyperresponsiveness of the airways can experience bronchoconstriction at the lowest dosages of Provocholine, or with the diluent alone. If severe bronchoconstriction occurs, it should be reversed immediately by the administration of a rapid-acting inhaled ß-agonist. Because of the potential for severe bronchoconstriction, Provocholine challenge should not be performed in any patient with low baseline FEV_1 of less than 1.5 litres or less than 70% of the predicted value. Please consult standard nomograms for predicted values.

Special Populations

Geriatrics: No data is available.

Pregnancy: 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.

Nursing Mothers: 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.

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

Laboratory Personnel: Provocholine aerosol may cause bronchoconstriction in laboratory personnel and others in the same room as the patient undergoing the test. Laboratory personnel with asthma or hay fever should take appropriate precautions when handling the material. (See SPECIAL HANDLING INSTRUCTIONS)

ADVERSE REACTIONS

Adverse reactions associated with inhaled methacholine challenge tests are rare, and include incidences of headache, throat irritation, light-headedness and itching.

A positive reaction to methacholine challenge may produce symptoms of bronchospasm, such as chest tightness, cough or wheezing.

Incidences of severe bronchoconstriction can be avoided by limiting the challenge test to cases of potentially mild asthma, in those patients with normal or near normal FEV_1, and by cautiously increasing the dosage.

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

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il
Additionally, you should also report to Kamada Ltd. to email address: pharmacovigilance@kamada.com

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

Precaution should be taken when the inhalation challenge is performed in patients receiving any ß-adrenergic blocking agents, as it is possible that bronchoconstriction may not reverse as readily.

The following asthma and hay fever medications inhibit the response of airways to Provocholine, and should be withheld before the test, for their duration of action: ß-agonists, anticholinergics and theophylline. Corticosteroids, cromoglycate and nedocromil, after regular use, may alter Provocholine responsiveness but they do not do this acutely; thus, they may be continued in their regular dose before any test. The effects of other newer medications have not been investigated.

Drug-Food Interactions

Methacholine chloride can be administered without regards to timing of meals.

Drug-Herb Interactions

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

Drug-Laboratory Test Interactions

The interactions of methacholine chloride with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Two methods of administration of the Provocholine (methacholine chloride powder for inhalation) inhalation challenge test 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, a constantly generated aerosol of Provocholine. By contrast, the dosimeter method requires the patient to take five full breaths of Provocholine aerosol generated to produce a specific dose per breath. With either technique, the test is stopped if the FEV_1 falls by more than 20% from the mean baseline FEV_1.

The concentration at dose and the percent fall in FEV_1 are then used to calculate either the provocative concentration to cause a fall in FEV_1 of 20% (PC_{20}), or the provocation dose (PD_{20}).

DOSAGES

Adults and children (5 years or older) are exposed to the following increasing concentrations of Provocholine: 0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 mg/mL. (See Table 1.)

PREPARATION OF DILUTIONS

All dilutions should be made with 0.9% sodium chloride injection containing 0.9% benzyl alcohol, as suggested in Table 1, in sterile Type I Glass vials. After adding the 0.9% sodium chloride solution, shake each vial to obtain a clear solution. Check the date of preparation or expiry before using dilutions that are not freshly prepared.

Provocholine solutions prepared using aseptic technique may be stored in a refrigerator (2° to 8°C) for up to 2 weeks. After this time, discard the vials and prepare new dilutions. Freezing does not affect the stability of the dilutions. 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.

Discard used solution from the nebulizer after each concentration.

Table 1 describes a method of producing appropriate dilutions, using a single 20 mL vial containing 100 mg of methacholine chloride.

Table 1: Preparation of Serial Dilutions Using a Single 100 mg Vial

TAKE Provocholine (Methacholine Chloride Powder for inhalation)	**ADD** NaCl 0.9% with 0.9% Benzyl alcohol	**OBTAIN DILUTION**
100 mg	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	0.06 mg/mL (I)
3 mL of dilution I	3 mL	0.03 mg/mL (J)

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.

ADMINISTRATION

The challenge test must be conducted in a pulmonary function laboratory or clinic, by adequately trained personnel, for safety and accuracy.

The FEV_1 value should be established before and after diluent inhalation. After determination of the post-diluent baseline pulmonary function, the predicted value of a positive response is then calculated from the mean before diluent inhalation.

The challenge is performed by giving a subject increasing serial concentrations of Provocholine, after determining baseline FEV_1 with inhaled normal saline control containing 0.9% benzyl alcohol. A subject to be challenged must have an FEV_1 of at least 70% of the predicted value. A common error giving inaccurate results is caused by not taking a full inspiratory breath prior to baseline FEV_1 determination. **Consult a physician if the FEV_1 falls below 1.5 litres. Do not leave the patient unattended at any time.**

Increasing concentrations of Provocholine are administered until there is a 20% fall in FEV_1 or the highest concentration of 16 mg/mL is reached.

When using the dosimeter method, one inhalation unit is defined as one inhalation of a solution of Provocholine containing 1 mg/mL. Because doses are taken in rapid succession, the units are expressed as cumulative breath units, as shown in Table 2, below.

Table 2: Cumulative Inhalation Units

Serial Concentration		Number of Breaths	Cumulative Units per Concentration	Total Cumulative Units
0.03	mg/mL	5	0.15	0.15
0.06	mg/mL	5	0.3	0.45
0.125	mg/mL	5	0.625	1.08
0.25	mg/mL	5	1.25	2.33
0.5	mg/mL	5	2.5	4.83
1	mg/mL	5	5	9.83
2	mg/mL	5	10	19.83
4	mg/mL	5	20	39.83
8	mg/mL	5	40	79.83
16	mg/mL	5	80	159.83

An inhaled ß-agonist must be administered after Provocholine challenge 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 ß-agonist. Patients should not be allowed to leave the laboratory until their FEV_1 has returned to within 90% of baseline.
In order to produce interpretable results, it is important to calibrate nebulizers to produce a standard output, and validate the reproducibility of the delivery system. Suitable nebulizers and standard settings are discussed in published sources.
Detailed instructions for carrying out the tidal breathing or the dosimeter methods are provided in the Product Monograph, as are alternative methods of calculating the PC_{20} (in mg/mL) or the PD_{20} (in cumulative µmoles or cumulative breath units).
Results can be interpreted with respect to the presence or absence of asthma only if the FEV_1/VC is >70%. The cut-off point between normal and increased responsiveness is a PC_{20} of 8 mg/mL, or a PD_{20} of 4 cumulative µmoles or 80 cumulative breath units. Increased responsiveness is arbitrarily graded as borderline if between 4 and 8 mg/mL (2 and 4 µmoles or 40 and 80 breath units), as mild between 2 and <4 mg/mL (1 and <2 µmoles or 20 and 40 breath units), as moderate if between 0.25 and <2 mg/mL (0.125 and <1 µmoles or 5 and <20 breath units), and as severe if <0.25 mg/mL (<0.125 µmoles or <2.5 breath units). Patients with a PC_{20} >16 mg/mL (or a PD_{20} >8 µmoles or >160 cumulative breath units) are unlikely to have current symptoms due to asthma. When the PC_{20} is between 2 and 16 mg/mL, or the PD_{20} is between 1 and 8 µmoles or 20 and 160 cumulative breath units, current symptoms due to asthma are likely to be mild, infrequent or absent. Current symptoms of asthma are usual when the PC_{20} is <2 mg/mL, or the PD_{20} is <1 µmoles or <20 cumulative breath units.

SHORTENING THE TEST PROCEDURE

Technicians should be well versed on the longer procedure before attempting a shorter version. Shortening the test does run the risk of inadvertently giving the patient too high a dose; always err on the side of safety and give a lower dose when in doubt. If clinical history suggests that the patient may not have asthma or that their asthma is very mild, then the lowest concentration may be omitted, as described below:

1. Starting Concentrations in Adults

As a guide, the first concentration of Provocholine can be based on the following criteria:

a) If FEV_1/VC >80% AND FEV_1 >70% predicted AND FEV_1 falls <10% after the diluent inhalation AND the patient's symptoms are **well controlled** on the following medications, use these starting concentrations:

Medication	Starting Concentration
Inhaled or ingested corticosteroids	0.125 mg/mL
Daily bronchodilators	0.25 mg/mL
Occasional bronchodilators (< once/day)	1.0 mg/mL
No medications	2.0 mg/mL

b) If FEV_1/VC <80% OR FEV_1 <70% predicted AND FEV_1 falls <10% after the diluent inhalation AND the patient's symptoms are **well controlled** on the following medications, use these starting concentrations:

Medication	Starting Concentration
Inhaled or ingested corticosteroids	0.03 mg/mL
Other or no medications	0.125 mg/mL

c) If a patient's FEV_1 falls by 10% or more after the diluent inhalation, or if asthma symptoms do not appear to be well controlled, **DO NOT** omit any concentrations, and start all patients at 0.03 mg/mL.

2. Starting Concentrations in Children

a) If FEV_1/VC >80% AND the child's symptoms are **well controlled** on the following medications, use these starting concentrations:

Medication	Starting Concentration
Inhaled or ingested corticosteroids	0.03 mg/mL
Daily or occasional bronchodilators	0.06 mg/mL
No medications	0.25 mg/mL

b) If FEV_1/VC <80% OR if asthma symptoms do not appear to be well controlled, **DO NOT** omit any concentrations, and start all patients at 0.03 mg/mL.

3. Omission of Concentrations

If, after the first concentration of Provocholine, there has been no evidence of any significant fall in the FEV_1 (less than 5% from mean baseline) and there is **NO** clinical evidence of any bronchoconstriction (chest tightness, cough or wheezing), the next dose may be omitted. As soon as there is any evidence of symptoms or a fall greater than 5% from mean baseline FEV_1, **DO NOT** omit any further concentrations. If a concentration is omitted, it is important to stress before every 2-minute inhalation that the subject should remove the face mask/mouthpiece as soon as they experience any breathing or chest discomfort.

OVERDOSAGE

Provocholine 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 IM or IV.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Methacholine chloride is the ß-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.

When a solution containing Provocholine is inhaled, subjects with current asthma are more sensitive to methacholine and bronchoconstrict at lower doses than healthy subjects. This difference in response is the pharmacologic basis for the Provocholine inhalation diagnostic challenge. The test is most useful diagnostically when there are current symptoms consistent with asthma and when the forced expiratory volume at one second (FEV_1) is normal at >70% predicted. A normal result excludes current asthma (variable airflow limitation), but does not exclude past asthma.

Pharmacodynamics

When there is chronic airflow limitation with an FEV_1/VC of <70%, the test can be abnormal due to other pathophysiological causes such as smoker's bronchitis, emphysema or cystic fibrosis. The challenge may also be positive in patients with allergic rhinitis without symptoms of asthma, or in patients who have had or will in the future develop asthma symptoms.

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

STORAGE AND STABILITY

Temperature:

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

Expiry date/shelf life:

- The expiry date of the product is indicated on the packaging materials.

Reconstituted Solutions:

- Provocholine Powder reconstituted with 0.9% saline with 0.9% benzyl alcohol as a preservative, using aseptic technique, may be stored under refrigeration (2° to 8°C) for up to 14 days. After this time, discard the vials and prepare new dilutions.
- Freezing does not affect the stability of dilutions made with Provocholine and 0.9% saline with 0.9% benzyl alcohol.

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.

When using Provocholine any unused solution should be discarded from the nebulizer after each concentration.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Provocholine Powder:

- 100 mg – in 20 mL amber glass vial in boxes of 6 vials.
- 0.9% saline with 0.9% benzyl alcohol must be used to reconstitute the powder (not included).
- Administered via inhalation using a nebulizer (not included).

Manufacturer: Pancap Pharma Inc
Markham, Ontario Canada, for
Methapharm Inc.
Brantford, Ontario Canada
Licence Holder: Kamada Ltd.
Beit Kama, Israel

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