Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methacholine chloride 100 mg Powder for nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial contains 100 mg methacholine chloride

3 PHARMACEUTICAL FORM

Powder for nebuliser solution

White or off-white powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Methacholine chloride is indicated in adults and children (5 years old and above) able to perform reproducible spirometry for the diagnosis of non-specific bronchial airway hyper-reactivity who do not have clinically apparent asthma but with a clinical history suggestive of the condition and with normal spirometry (see section 4.2 and section 5.1).

4.2 Posology and method of administration

Medicinal product subject to restricted medical prescription.

Posology

Adults and children (aged 5 years and above):

Methacholine chloride is administered only in solution for inhalation.

Before starting a Methacholine chloride 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 60% of the predicted value (in adults and children) and greater than or equal to 1.5 L (in adults).

At commencement of the Methacholine chloride challenge test and prior to nebulisation with Methacholine chloride, FEV_1 should be measured following exposure to nebulised diluent (post-diluent FEV_1). The methacholine challenge test is considered positive if there is a reduction in FEV_1 of 20% or more from FEV_1 with the recommended diluent. The test should be stopped at this point. The reduction value must be calculated and recorded before starting the test with Methacholine chloride.

Paediatric population
The safety and efficacy of Methacholine chloride in children under 5 years of age has not been established. No data are available.

Directions for Reconstitution and Dilution Prior to Administration
Note: Do not inhale the powder. Do not handle this product if you suffer from asthma or allergies. All dilutions must be made with 0.9% sodium chloride solution for injection, using empty, sterile borosilicate Type I glass vials. After adding the sodium chloride solution, shake each vial until you obtain a clear solution.

Preparation of Serial Dilutions:
Refer to Table 1A and Table 1B for the preparation of serial dilutions of Methacholine chloride for doubling concentrations/doses and quadrupling concentrations/doses, respectively.

Table 1A: Preparation of serial dilutions using a single vial of Methacholine chloride powder (100 mg) for nebuliser solution (methacholine chloride) - doubling concentrations or doses.

Take	ADD 0.9% SODIUM CHLORIDE	Methacholine chloride Concentration	Methacholine chloride Dose*
100 mg Methacholine chloride	6.25 mL	16 mg/mL (A)	380 micrograms
3 mL of dilution A	3 mL	8 mg/mL (B)	190 micrograms
3 mL of dilution B	3 mL	4 mg/mL (C)	95 micrograms
3 mL of dilution C	3 mL	2 mg/mL (D)	47.5 micrograms
3 mL of dilution D	3 mL	1 mg/mL (E)	23.75 micrograms
3 mL of dilution E	3 mL	0.5 mg/mL (F)	11.875 micrograms
3 mL of dilution F	3 mL	0.25 mg/mL (G)	5.938 micrograms
3 mL of dilution G	3 mL	0.125 mg/mL (H)	2.969 micrograms
3 mL of dilution H	3 mL	0.0625 mg/mL (I)	1.484 micrograms
3 mL of dilution I	3 mL	0.0312 mg/mL (J)	0.742 micrograms

*The Methacholine chloride dose corresponding to each Methacholine chloride concentration was determined based on the dose delivered from the English Wright nebuliser for two (2) minutes of nebulisation using dry compressed air to power the nebuliser, with a pressure regulator set to 50 lb/in^2 to produce an output within 10% of 0.13 mL/min−1 (or g/min-1) (measured gravimetricallly). The English Wright nebuliser generates aerosol with particles between 1.0 and 1.5 micrometers aerodynamic particle mass median diameter (MMD). Nebulisers with MMD between 1.0 and 3.6 micrometers do not influence the response. Other suitable nebulisers may be used as long as the device output and particle size are characterized (or the nebuliser is known to deliver an aerosol with MMD between 1.0 and 3.6 micrometers), and the dose is calculated (see Method of administration).

Table 1B: Preparation of serial dilutions using a single vial of Methacholine chloride powder (100 mg) for nebuliser solution (methacholine chloride) - quadrupling concentrations or doses.

Take	ADD 0.9% SODIUM CHLORIDE	Methacholine chloride Concentration	Methacholine chloride Dose*
100 mg Methacholine chloride	6.25 mL	16 mg/mL (A)	380 micrograms
3 mL of dilution A	9 mL	4 mg/mL (B)	95 micrograms
3 mL of dilution B	9 mL	1 mg/mL (C)	23.75 micrograms
3 mL of dilution C	9 mL	0.25 mg/mL (D)	5.938 micrograms
3 mL of dilution D	9 mL	0.0625 mg/mL (E)	1.484 micrograms

*The Methacholine chloride dose corresponding to each Methacholine chloride concentration was determined based on the dose delivered from the English Wright nebuliser for two (2) minutes of nebulisation using dry compressed air to power the nebuliser, with a pressure regulator set to 50 lb/in^2 to produce an output within10% of 0.13 mL·min−1 (or g/min-1) (measured gravimetically). The English Wright nebuliser generates aerosol with particles between 1.0 and 1.5 micrometers aerodynamic particle mass median diameter (MMD). Nebulisers with MMD between 1.0 and 3.6 micrometers do not influence the response. Other suitable nebulisers may be used as long as the device output and particle size are characterized (or the nebuliser is known to deliver an aerosol with MMD between 1.0 and 3.6 micrometers), and the dose is calculated (see Method of administration).

Use a sterile hydrophilic bacterial-retentive filter of pore size 0.22 micrometers (Millex GV 0.22 micrometers) when transferring the solution from each vial (at least 2 mL) to thenebuliser.

Method of administration

The testing should only be conducted under specialist medical supervision by a doctor familiar with all aspects of the methacholine challenge test, see section 4.4.

1. Dosing

Quadrupling increments are recommended for clinical testing, but if methacholine challenge testing is used to determine changes in airway reactivity following therapy in patients known to have asthma, using doubling doses will give more precise PD20 values.

2. Tidal Breathing Method:

For clinical studies conducted with Methacholine chloride using the tidal breathing method, the currently obsolete English Wright nebuliser was operated using dry compressed air to power the nebuliser, with a pressure regulator set to 50 lb/in^2 to produce an output within 10% of 0.13 mL/min−1 (or g/min−1) (measured gravimetrically) and a nebulisation time of two (2)

minutes. The English Wright nebuliser generates aerosol with particles between 1.0 and 1.5 micrometers aerodynamic particle mass median diameter (MMD). MMD between 1.0 and 3.6 micrometers is acceptable.

The following tidal breathing method is based on the use of the currently available Hudson RCI MicroMist Small Volume Nebuliser using dry compressed air to power the nebuliser, with a pressure regulator set to 50 lb/in^2 (psi) and flow controller set to a flow rate of 4.5 LPM (litres per minute) with a nebulisation time of **one (1) minute**.

- Under these conditions, the device output was within 10% of 0.13 mL/min−1 (or g/min−1) (measured gravimetrically) similar to that of the English Wright nebuliser conditions used in the clinical studies.
- The measured MMD was found to be 3.4 micrometers, i.e. within the acceptable range of MMD of 1.0 – 3.6 micrometers.
- Using the Hudson RCI MicroMist Small Volume Nebuliser, the delivered dose of the respirable fraction for the 16 mg/mL Methacholine chloride solution was about 380 microgram, the same as shown in Table 1A and Table 1B.

1. Use the Hudson RCI MicroMist Small Volume Nebuliser and dry compressed air to power the nebuliser.

2. Using a 3 mL syringe and needle, draw up 2-3 mL of the diluent (0.9% Sodium Chloride) and place it in the nebuliser vial. Attach the nebuliser and necessary tubing to the dry compressed air source.

3. At this time, the subject should be told that subsequent aerosols may produce mild cough, chest tightness or shortness of breath. Tell the subject that if these symptoms become uncomfortable, to remove the face mask or mouthpiece and to stop inhaling the aerosol immediately. Try to avoid suggesting that these symptoms will definitely develop, as suggestion alone can lower the FEV[1]. Remember that perception of airway narrowing can vary considerably between subjects, making it advisable to watch and listen for other signs such as wheeze and an altered pattern of breathing. Instructions to cease inhaling the aerosol if symptoms become troublesome should be repeated before every dose.

4. Instruct the patient to relax and breathe the aerosol quietly (tidal breathing) for 1 minute.

5. Place the face mask loosely over the nose and mouth or the mouthpiece in the mouth (with a nose-clip) of the patient. The nebuliser should be kept vertical. The patient should hold the nebuliser so as to avoid warming the solution, and subsequently altering the output.

6. Set the pressure regulator to 50 lb/in^2 (psi) and start the nebuliser by setting the flow controller to a flow rate of 4.5 LPM. Start the stopwatch immediately.

7. After exactly one minute, turn off the nebuliser and flow-meter, remove the face mask or mouthpiece from the patient, and discard the remainder of the solution in the nebuliser.

Measure the FEV_1 30 and 90 seconds after the end of the inhalation. These values may be left at ambient (spirometer) temperature pressure saturated (ATPS). If the post-diluent FEV_1 falls by 20% or more from the mean baseline FEV_1, do not give further inhalations and proceed with Step 10. If the post-diluent FEV_1 falls by less than 20%, proceed with Step 8.

8. The dose/concentration of the first aerosol of Methacholine chloride for themethacholine challenge test is either 1.484 microgram/0.0626 mg/mL (for quadruplingdosing) or 0.742 microgram/0.0312 mg/mL (if doubling dosing). Subsequent doses are given at 5-minute intervals in doubling orquadrupling doses/concentrations as per dosing increments described in Table 1A or Table 1 B.

9. Repeat steps 1 through 8 with each increasing dose/concentration of Methacholine chloride untilthe FEV_1has fallen by 20% or more from the post-diluent FEV_1, or the highest dose/concentration in Table 1A or Table 1B has been given. At this point, do not give any further aerosols of Methacholine chloride. Note the last and second last dose of Methacholine chloride prior to discontinuing inhalations.

10. After the test is completed, give the patient 2 puffs of a ß-agonist. Wait 10 minutes and measure the FEV_1 and VC (Vital Capacity). Patients should not be allowed to leave the laboratory until their FEV_1 has returned to within 90% of baseline.

After testing with Methacholine chloride, a beta-agonist may be administered to speed up the return to the FEV_1 baseline value and to alleviate any patient discomfort. The majority of patients revert to normal pulmonary function within 5 minutes after administration of a bronchodilator or within 30 – 45 minutes without a bronchodilator.

The European Respiratory Society (ERS) technical standard on bronchial challenge testing provides that other suitable nebulisers may be used as long as the device output and particle size are characterized to enable the calculation of dose. Knowledge of the device relating to deviceoutput per minute, the particle size distribution, time of tidal breathing and the ratio of inspiratory time to total breathing time will enable the calculation of the Methacholine chloride dose.

Substituting nebuliser devices with different characteristics (output rate and particle size distribution) would be expected to deliver a different methacholine 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 methacholine in terms of dose/PD_{20}, and not concentration/PC_{20}.

Calculation and Interpretation of Results:
Either the provocative dose or the provocative concentration, causing a 20% fall in FEV_1(PD_{20} or PC_{20}) may be calculated as described below:

1. Calculation of PD_{20}
Calculate the PD_{20} as follows:

$$PD20 = antilog\,[logD1 + \frac{(\log D2 - logD1)(20 - R1)}{(R2 - R1)}]$$

Where:
D1 = second last Methacholine chloride dose (< 20% FEV_1decrease)
D2 = last Methacholine chloride dose (> 20% FEV_1 decrease)
R1 = % FEV_1decrease after D1
R2 = % FEV_1 decrease after D2

2. Calculation of PC_{20}
With the tidal breathing method, airway responsiveness may be expressed as that concentration of Methacholine chloride provoking a fall in FEV_1 of 20% (PC20). The percent fall in FEV_1can be calculated using the mean baseline FEV_1, as shown below:

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

% fall in FEV_1 is then plotted against the rising concentration of Methacholine chloride (log scale). The PC_{20} is obtained by linear interpolation between the last two points, as shown in Figure 1 below.

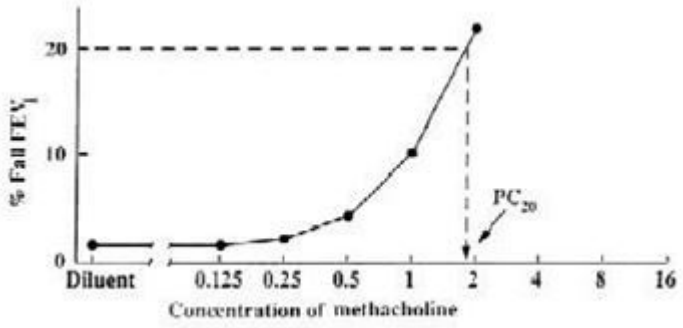

Figure 1: Calculation of PC_{20}

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

$$PC20 = antilog\,[logC1 + \frac{(\log C2 - logC1)(20 - R1)}{(R2 - R1)}]$$

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

3. Interpretation of Results

A negative (normal) methacholine challenge result is defined as a FEV_1 reduction of less than 20% after all of the doses have been administered (the ERS technical standard on bronchial challenge testing also defines a negative methacholine challenge test as a PD20 > 380 microgram, PC20 > 16 mg/mL).

4.3 Contraindications

Methacholine chloride is contraindicated in the following cases:

- Hypersensitivity to the active substance or other parasympathomimetic agents.
- In children under 5 years of age.
- Clinically apparent asthma, wheezing or with results at or below the limit in the baseline respiratory function tests (patients with a baseline FEV_1 less than 60% of predicted (in adults and children) and with a baseline FEV_1 less than 1.5 L (in adults).
- Patients treated with beta blockers, since the response to methacholine chloride can be emphasized or prolonged and the patient may not respond easily to the treatment used for the restoration of respiration and alleviation of symptoms.
- Repeated administration of Methacholine chloride through inhalation of doses higher than the dose administered on the day of the diagnostic test is contraindicated.
- Bradycardia
- Known aortic aneurysm
- Myocardial infarction or stroke in the last 3 months.
- Uncontrolled hypertension.
- Patient with myasthenia gravis undergoing treatment with cholinesterase inhibitors.
- Recent eye surgery or intracranial pressure elevation risk
- Pulmonary embolism
- Pregnancy
- Breast feeding

4.4 Special warnings and precautions for use

General

To ensure the safe and effective use of challenge testing with Methacholine chloride, patients should be informed about the symptoms that may occur as a result of the testing and how to manage them.

Take full clinical respiratory history, before embarking on methacholine challenge, given the occurrence of false positive test results with methacholine in other respiratory conditions, such as after influenza, upper respiratory tract infections or immunisations, in very young or very old patients or in patients with chronic pulmonary diseases (cystic fibrosis, sarcoidosis, tuberculosis, chronic obstructive pulmonary disease). Challenge testing can be positive in patients with allergic rhinitis without asthma, in smokers, or in patients exposed to aerial contaminants.

It is essential that the baseline spirometry is accurate. If the baseline spirometry is not performed or measured accurately, and the initial FEV1 is underestimated, subsequent falls after inhaling Methacholine chloride solutions may not be detected, resulting in too high dose and excessive bronchoconstriction.

Unacceptable methacholine challenge test manoeuvres may result in false-positive results.

Route of administration

Methacholine chloride is to be administered only by inhalation.

Patients

Administration of Methacholine chloride to patients with epilepsy, cardiovascular disease, vagotonia, peptic ulcer, thyroid disease, urinary tract obstruction or other conditions that could be adversely affected by a cholinergic agent should only be carried out if the doctor deems that the risk/benefit ratio to be positive for the patient.

As a result of the administration of Methacholine chloride severe bronchoconstriction and a reduction in respiratory function may occur. Patients with airway hyper-reactivity can experience bronchoconstriction with doses as low as 0.031 mg/mL. If severe bronchoconstriction occurs, this must be immediately reversed by administration of a rapid-acting inhaled bronchodilator agent (beta-agonist).

Subjects who suffer from asthma are noticeably more sensitive to bronchoconstriction induced by methacholine than healthy subjects. Caution is required in patient with brittle asthma.

Medical personnel

The challenge testing for Methacholine chloride must only be carried out under specialist medical supervision by a doctor familiar with all aspects of the methacholine inhalation challenge testing technique, all contraindications, warnings and precautions, and the management of respiratory failure. The doctor responsible for the testing must be contactable while it is being carried out and available immediately if needed. If the doctor is carrying out the testing himself, another person must be available to assist him if needed. The patient must never be left unattended during the testing. Emergency equipment and medication must be available immediately to treat acute respiratory failure.

Laboratory staff with asthma or allergies should be particularly careful and take necessary measures when handling the material or if they are performing testing on patients, see section 6.6.

Paediatric population

Children are also more likely to exhibit positive results due to non-asthmatic increased airways responsiveness. Therefore, it is important for Physicians to make sure other possible respiratory conditions are also reviewed in this context.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant treatment of Methacholine chloride and beta blockers is contraindicated, see section 4.3.

The following medications in Table 2 for the treatment of asthma inhibit the airways' response to Methacholine chloride, whereby their treatment must be interrupted before the testing, due to the duration of their effect: beta agonists, antimuscarinics and theophylline (see the table below for more information). The effects of more recent new medications have not been investigated, see section 4.4.

Methacholine challenge should only be considered for patients on regular asthma medication if the accuracy of the diagnosis is in doubt. Methacholine challenge should be conducted after supervised withdrawal of the asthma medication and provided normal spirometry persists. The possibility of rebound airways' hyperresponsiveness after withdrawal of asthma treatment should also be borne in mind in interpretation of test results.

Table 2: Medications which may decrease airway hyperresponsiveness and withholding time

Medications	**Min. time interval from the last dose to the challenge testing (hrs)**
Short-acting β-agonists in conventional inhaled doses (e.g. Salbutamol 200 micrograms)	6
Long-acting β-agonists (e.g. salmeterol)	36
Ultra-long-acting β-agonists (e.g. indacaterol, vilanterol, olodaterol)	48
Ipratropium (Atrovent 40 micrograms)	12
Long-acting anti-muscarinic agents	≥ 168
Oral theophylline	12-48

Cromones, inhaled corticosteroids and leukotriene modifiers have little or no effect in single dose, and do not need to be withheld before testing unless the intent is to offload an anti-inflammatory effect; duration of effect after regular use is uncertain but a withhold time of 4–8 weeks is reasonable.

Normal dietary servings of caffeine and caffeine-related products (e.g. chocolate) have no effect of clinical significance. Tobacco smoking should be avoided 1 hour prior to the test.

4.6 Fertility, pregnancy and lactation

Pregnancy
There have been no animal reproduction studies with methacholine chloride. It is not known whether methacholine chloride can cause harm to the foetus when administered to pregnant patients. An inadequate oxygen supply during pregnancy can be harmful to the child. Methacholine chloride must not be used during pregnancy.

Breast-feeding
It is unknown whether methacholine chloride is excreted in human milk.

Fertility
It is not known whether methacholine chloride affects fertility.

4.7 Effects on ability to drive and use machines

Methacholine chloride has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The adverse reactions are classified by System Organ Class and frequency defined as follows: Very Common (≥ 1/10); Common (≥ 1/100, <1/10); Uncommon (≥ 1/1,000, <1/100); Rare (≥ 1/10,000, <1/1,000); Very Rare (<1/10,000), not known (cannot be estimated from the available data). Undesirable effects were associated with 153 inhaled methacholine chloride challenge tests.

Nervous System Disorders
Not known: Headache, dizziness

Respiratory, thoracic and mediastinal disorders
Not known: Throat irritation
Not known: Bronchoconstriction
Not known: Bronchospasm, chest tightness, cough, wheezing

Skin and subcutaneous tissue disorders
Not known: Itching

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Methacholine chloride is administered only by inhalation. When administered orally or by injection overdose of methacholine chloride can cause syncope, with cardiac arrest and loss of consciousness. Serious toxic reactions should be treated with 0.5 – 1 mg of atropine sulphate, administered IM or IV.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other diagnostic agents, ATC code: V04CX03

Mechanism of action

Methacholine chloride is the β-methyl derivative of acetylcholine and differs from this principally in its long duration and selectivity of action. Bronchial smooth muscle contains significant parasympathomimetic (cholinergic) innervation.

The pharmacological basis for the challenge testing with methacholine chloride in solution is that subjects who suffer from asthma are noticeably more sensitive to induced bronchoconstriction than healthy subjects.

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

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.

Compared with acetylcholine, methacholine chloride is hydrolysed more slowly by acetylcholinesterase, being practically resistant to inactivation by nonspecific cholinesterase or pseudocholinesterase.

Methacholine chloride has a strong affinity for muscarinic receptors which play a dominant role in smooth muscle contraction and unlike acetylcholine, has a weak affinity for nicotinic receptors. Therefore, methacholine chloride has a greater selectivity for its pharmacological action for bronchoconstriction.

Clinical efficacy and safety

Methacholine challenge aims to detect bronchial airways hyperreactivity which can present in association with other respiratory conditions and is not itself diagnostic of asthma. However, methacholine challenge is most useful to exclude an asthma diagnosis. In 1,500 asthma patients and 500 non-asthma patients (both atopic and non-atopic), 90% of the asthmatic patients had a medium or highly positive response to methacholine chloride. Less than 5% of individuals with allergies or non-atopic control subjects demonstrated a highly positive response. 27% of patients with allergies had a negative response compared to 49% of control subjects. Patients with allergies and healthy patients had a similar incidence of positive responses. 30% of patients with allergies had a medium-positive response compared with 18% of healthy patients with a family history of asthma and 8% of control subjects with a healthy family history. Differences were observed with healthy subjects where there is no family history of asthma.

Amongst the asthmatic patients, the severity of the asthma determined the bronchial sensitivity of the subjects to the challenge testing with methacholine. The sensitivity varied from 100 to several thousand times compared with that of normal subjects. However, in ex-asthmatic subjects, the level of bronchoconstriction was also related to the severity of previous asthmatic symptoms. The average sensitivity of ex-asthmatic subjects was, approximately, one tenth compared to asthmatic subjects.

In population studies, the prevalence of hyper-reactivity tomethacholine chloride ranges from 8 to 15%. Whilst the sensitivity level ofasthmatic subjects is similar to that of non-asthmatic subjects, asthmaticsubjects respond to average lower doses. Less sensitive asthmatic subjectsgenerally have moderate, more stable diseases.

A study investigating whether prostaglandin synthesis produces methacholine tolerance, revealed that the attenuation of methacholine's effect with repeated testing is not due solely to prostaglandin synthesis and must involve, in part, other mechanisms, such as changes in methacholine deposition, agonist-receptor interactions, or post-receptor responses. In addition, prostaglandin inhibitors may increase baseline methacholine responsiveness in healthy non-asthmatic subjects.

Using a maximal methacholine concentration of 16 mg/mL in a study that assessed methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma, had shown no serious adverse reactions developed by the participants in the study.

Paediatric population

A study evaluated methacholine sensitivity in 166 young subjects (mean age 10 years, range 5 to 22 years) who had normal resting spirometry but who presented with signs and symptoms suggesting lower airways hyperreactivity. Nine concentrations of methacholine from 0.075 to 25 mg/ml were used. The challenge test confirmed the severity of symptoms of asthma which matched the sensitivity to methacholine. Children who were positive were more likely to be receiving asthma therapy at the 1-year follow up.

5.2 Pharmacokinetic properties

The extent of systemic absorption of methacholine after inhalation in humans is unknown due to an absence of pharmacokinetic data.

5.3 Preclinical safety data

The acute and sub-acute inhalation toxicity of methacholine chloride to cyanomologus monkeys was assessed by exposure of animals to methacholine solution. Studies of inhaled administration of methacholine chloride for 7 days in monkeys (0.02, 0.08 and 0.4 mg/kg) led to expected dose-dependent bronchoconstriction.

The acute response was characterised by changes in lung function after 2 – 3 minutes of exposure and complete recovery after 30 minutes following termination of an exposure.

The sub-acute inhalation toxicity of methacholine was assessed by single daily aerosol exposure of the monkeys to graded doses of methacholine for 7 days. There were no haematological or biochemical changes which could be attributed to exposure to methacholine. Nor were there treatment-related histopathological changes observed in exposed animals. There were changes observed in the mechanical characteristics of the lungs of the animals exposed to methacholine for 7 days.

There are no data on genotoxicity. No long-term animal studies of the carcinogenic effect of methacholine chloride have been performed. In addition, no reproductive toxicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

- Un-reconstituted vials (powder): 3 years.

Reconstituted vials can be stored and used within 28 days if refrigerated, discard any remainder.

6.4 Special precautions for storage

- Un-reconstituted vials (powder): This medicinal product does not require any special storage conditions.
- Reconstituted vials: Reconstituted and diluted solutions of the medicinal product can be stored and used within 28 days if refrigerated discard any remainder. (Refer to Section 6.3)

6.5 Nature and contents of container

Methacholine chloride is presented in a Type I 20 mL amber glass vial with bromobutyl rubber stopper and a flip-off cap, containing 100 mg of methacholine chloride, packed in a carton containing 6 vials.

6.6 Special precautions for disposal and other handling

Methacholine chloride 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 Methacholine chloride aerosol from being released into the air of the room.
The reconstituted Methacholine chloride solution is a clear and colourless solution free from foreign particles. Reconstituted vials can be used within 28 days if refrigerated. Any unused liquid should be disposed of safely.
When using Methacholine chloride, any unused solution should be discarded from the nebuliser after each concentration. After the test, reusable nebulisers should be sterilized according to manufacturer's recommendations. Disposable nebulisers should be discarded appropriately.

7 MARKETING AUTHORISATION HOLDER

Methapharm Limited
The Black Church
St Mary's Place
Dublin 7
D07 P4AX
Ireland

8 MARKETING AUTHORISATION NUMBER

PA25355/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th June 2020

Date of last renewal: 17th January 2025

10 DATE OF REVISION OF THE TEXT

September 2024