- Bronchodilator Agent -

MEPTIN® 0.3 mL Unit
MEPTIN® 0.5 mL Unit
< Procaterol Hydrochloride >

Inhalation Solution

COMPOSITION
1. Composition

	MEPTIN® Inhalation Solution 0.3 mL Unit	MEPTIN® Inhalation Solution 0.5 mL Unit
Active ingredient	100 μg of procaterol hydrochloride/mL	
Contents	0.3 mL/unit[1)]	0.5 mL/unit[2)]
Inactive ingredients	Anhydrous citric acid, sodium hydroxide (pH adjuster), purified water	

1) Procaterol hydrochloride 30 μg
2) Procaterol hydrochloride 50 μg

2. Product Description

	MEPTIN® Inhalation Solution 0.3 mL Unit	MEPTIN® Inhalation Solution 0.5 mL Unit
Description	These products are clear, colorless liquids. They have no odor.	
pH	3.0 – 4.0	
Container	 Approx. 84 (L) × 11 (W) × 8 (H) mm	
	Blue plastic ampoule (PE)	Clear plastic ampoule (PE)

INDICATIONS
Remission of various symptoms caused by respiratory obstructive disturbance from the following diseases:
moderate acute asthma.

Contraindications (This drug is contraindicated in the following patients.)
Patients with a history of hypersensitivity to any ingredient of this drug.

DOSAGE AND ADMINISTRATION
The usual adult dose is 30-50 μg of procaterol hydrochloride (0.3-0.5 mL of MEPTIN® Inhalation Solution) via a nebulizer with deep breathing. For children, the amount should be reduced to 10-30 μg of procaterol hydrochloride (0.1-0.3 mL of the drug).
The dosage may be adjusted according to the patient's age and severity of symptoms.

< Precautions >
Patients and parents should be cautioned about the possible risk of serious adverse reactions, including arrhythmia and cardiac arrest, that may result from excessive use of this drug. The following information or other appropriate instruction should be given to patients receiving this drug or their families. (See **7. Overdosage**.)
Take this medication exactly as directed: 0.3-0.5 mL per dose for adults and 0.1-0.3 mL per dose for children.

PHARMACOLOGY
1. Bronchodilative Action
- The bronchodilative action of procaterol hydrochloride was comparable to or more potent than that of isoproterenol and more potent than that of salbutamol and orciprenaline, as determined by inhibition on increased pulmonary resistance in dogs, cats, and guinea pigs.
- The onset of the bronchodilative action is observed 1 to 5 minutes after inhalation in conscious guinea pigs and anesthetized dogs, indicating much faster onset of action than the tablet formulation.
- Inhaled procaterol hydrochloride dilates not only the central airway but also peripheral airways in pediatric asthma patients.

2. Duration of Bronchodilative Action
- Procaterol hydrochloride had a longer duration of bronchodilative action than isoproterenol, trimetoquinol, orciprenaline, and salbutamol in dogs, cats, and guinea pigs.
- The potency with which procaterol hydrochloride at 10 μg by inhalation inhibits the increase in airway resistance due to histamine is equal to that of salbutamol at 200 μg by inhalation in anesthetized dogs. However, procaterol is longer acting than salbutamol.

3. Selectivity for β_2-Adrenergic Receptors (Organ Selectivity)
The selectivity of procaterol hydrochloride for β-adrenergic receptors in the respiratory system was greater than that for such receptors in the cardiovascular system, as compared to isoproterenol, trimetoquinol, orciprenaline, and salbutamol in dogs, cats, and guinea pigs.

4. Anti-allergic Action

Procaterol hydrochloride exhibited a definite anti-allergic action by inhibiting antigen-induced increase in airway resistance, the PCA reaction, and histamine release from sensitized lung tissues in guinea pigs and rats, as well as allergen-induced skin reactions, and increases in asthmatic responses to allergen inhalation in bronchial asthma patients, as compared to isoproterenol, trimetoquinol, orciprenaline, and salbutamol.

5. Effects on Respiratory Tract System

Procaterol hydrochloride accelerated ciliary movement in airways of pigeons.

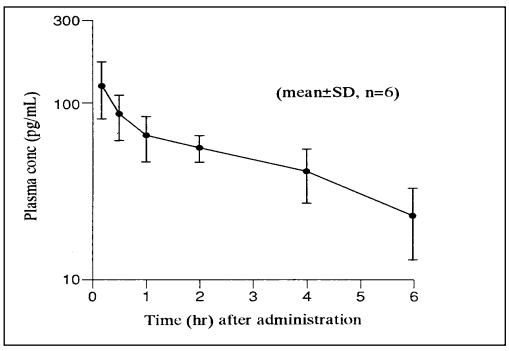
6. Effect on Exercise-Induced Asthmatic Attacks

Procaterol hydrochloride suppressed treadmil exercise-induced asthmatic attacks in patients with bronchial asthma.

PHARMACOKINETICS

1. Plasma Concentrations

When MEPTIN® Air was administered by inhalation to 6 healthy male subjects as 4 doses (40 μg per subject as procaterol hydrochloride[Note]), a peak plasma concentration of 128 pg/mL was attained at 15 min post-dosing, followed by a gradual decline.



2. Urinary Excretion

When MEPTIN® Air was administered by inhalation as 4 doses (40 μg per subject as procaterol hydrochloride), 14.36% of the dose was excreted in the urine within 24 hours post-dosing.

3. Cytochrome P450 Isozyme for Hepatic Oxidized Metabolism of Drugs

The enzyme is mainly CYP3A4 (*in vitro*).

Note: The approved dose for a single administration of MEPTIN® Air is 20 μg.

PRECAUTIONS

1. **Careful Administration (MEPTIN® Inhalation Solution should be administered with care in the following patients.)**

(1) Patients with hyperthyroidism (The disease may be exacerbated.)

(2) Patients with hypertension (Blood pressure may further increase.)

(3) Patients with heart disease (Palpitation, arrhythmia, exacerbation of heart disease, and other symptoms may occur.)

(4) Patients with diabetes mellitus (The disease may be exacerbated.)

(5) Patients who are pregnant or suspected of being pregnant (See **Use during Pregnancy or Lactation**.)

2. Important Precautions

(1) Continuous use of excessive amounts of this drug may cause cardiac arrhythmia and cardiac arrest. Special care should therefore be taken not to exceed the recommended dose of this drug at the time of asthma episodes.

(2) If the desired therapeutic effect of this drug cannot be achieved at the recommended dose, the drug should be discontinued. When the drug is administered to children, they should be properly instructed on the method of use of this drug and adequately observed for any effects.

(3) Patients and their families should be instructed to consult a physician for emergency treatment and reassessment of therapy when the recommended dosing schedule is not effective in relieving severe episodes of asthma.

3. Use in the Elderly

Dosage adjustment or other appropriate measures should be considered when prescribing this drug to elderly patients because these patients may be physiologically more sensitive to the drug than younger patients.

4. Use during Pregnancy, Delivery or Lactation

(1) This drug should be administered to pregnant or possibly pregnant women only if the expected therapeutic benefit is thought to outweigh any possible risk. (The safety of this drug during pregnancy has not been established.)

(2) Nursing should be interrupted before starting treatment with the drug. [Rat studies showed that procaterol hydrochloride is excreted in breast milk.]

5. Pediatric Use

The safety of this drug in low birth weight infants, neonates, and suckling infants has not been established.

6. Effects on Laboratory Tests

This drug tends to inhibit skin reactions in allergen tests. The drug should be withdrawn 12 hours prior to such tests.

7. Overdosage

(1) Administration of this drug to patients in excess of the recommended dose can cause ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation, and other symptoms), cardiac arrest, and other severe adverse reactions. Patients should be properly instructed on the dose and method of administration of the drug. (See **Precautions in Dosage and Administration** and **Important Precautions**.)

(2) Over dosage with this drug has been associated with tachycardia, tachycardiac arrhythmia, hypotension, nervousness, tremor, hypokalemia, and hyperglycemia. In the event any over dosage-related abnormalities are observed, the drug should be discontinued and, if required, gastric lavage should be performed to remove

any unabsorbed drug. Emergency treatment and general maintenance therapy should also be provided if needed. In the event serious tachycardiac arrhythmia has developed, β-blockers such as propranolol may be effective but administration of these drugs to asthma patients should be performed with care because β-blockers may increase airway resistance in these patients.

8. Precautions Concerning Use

(1) **At time of dispensing:**

Patients or their guardians should be instructed to keep the drug out of the reach of children to avoid accidental ingestion.

(2) Patients receiving this drug should be advised to rinse the mouth after inhalation whenever feasible.

(3) Patients should be instructed not to open the unit-dose ampoules until immediately before use, since the product contains no preservatives

(4) Patients should be instructed to use the entire contents of a unit-dose ampoule at one time and not to use the product for dose adjustment

(5) Combination of this drug with benzypenicillin Potassium should be avoided in view of the high probability of white turbidity being produced.

9. Other Precautions

(1) Tissue damage in cardiac muscle was noted in oral toxicity study of procaterol hydrochloride using rats and dogs, similar to other β_2-adrenergic agonists.

(2) Dietary administration of procaterol hydrochloride for 104 weeks was reported to cause mesovarian leiomyoma in SD rats. However, this tumor is rat species specific and tends to develop during long-term administration of β_2-adrenergic agonists.

ADVERSE REACTION

In clinical trials involving 6,655 subjects, a total of 101 patients (1.52%) showed adverse reactions including abnormal laboratory values [Figures represent total cases reported at the time of approval of the initial application and completion of reexamination for inhalation formulations: MEPTIN® Air, MEPTIN® Kid Air, and MEPTIN® Inhalation Solution (excluding MEPTIN® Inhalation Solution 0.3 mL and 0.5 mL Units)]. The following summary of data includes adverse reactions reported after marketing without data on the incidence.

* MEPTIN® Kid Air is not on the market in Indonesia

(1) Clinically significant adverse reactions (incidence unknown*)

1) Shock, anaphylactoid reactions: Shock or anaphylactoid reactions may occur. Patients should therefore be closely monitored. If abnormal findings are observed, the drug should be discontinued and appropriate measures taken.

2) Significant decreases in serum potassium levels have been reported in patients receiving procaterol hydrochloride. If xanthine derivatives, corticosteroids, or diuretics are coadministered with this drug to patients with severe asthma, extreme care is necessary to minimize the possibility of aggravating the decrease in serum potassium levels induced by β_2-adrenergic agonists. Serum potassium levels should be closely monitored for hypoxic patients, in view of the possible aggravation of cardiac arrhythmias secondary to a decrease in serum potassium levels.

(2) Other adverse reactions

	5% >; ≥0.1%	<0.1%	Incidence unknown*
Cardiovascular	Palpitation and tachycardia	Abnormal ECG, increase in blood pressure, facial flushing, etc.	Supraventricular extrasystole, supraventricular tachycardia, ventricular extrasystole, etc., facial pallor, and decrease in blood pressure
Psychoneurologic	Tremor, headache, and dull headache	Muscle cramp, numbness of hands, dizziness, cold sweat, sleepiness, etc.	Nervousness
Gastrointestinal	Nausea, vomiting, etc.		
Respiratory		Abnormal tracheal or pharyngolaryngeal sensation, nasal obstruction, dyspnea, etc.	
Hypersensitivity (note)		Skin rash, pruritis, etc.	
Other		Generalized malaise, weakness, impaired hearing, thrombocytopenia, etc.	Transient decrease in serum potassium (1-2 hr after dosing)

Note 1) If symptoms of hypersensitivity occur, the drug should be discontinued immediately.

*The incidences of adverse reactions reported voluntarily after marketing or those reported in foreign countries are not known.

DRUG INTERACTIONS

(1) Precautions for coadministration (MEPTIN® Inhalation Solution should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Catecholamines (e.g., epinephrine and isoproterenol)	The combined use of this drug with catecholamines may cause arrhythmias or, in some cases, cardiac arrest.	Epinephrine, isoproterenol, and other catecholamines potentiate adrenoreceptor stimulating action of this drug, possibly resulting in the induction of arrhythmias.

Xanthine derivatives (e.g., theophylline, aminophylline, and diprophylline)	The combined use of this drug with xanthine derivatives may aggravate hypokalemia and cardiovascular adverse reactions (e.g., tachycardia, arrhythmias) due to β-adrenergic stimulations. If any of these abnormalities are observed, appropriate measures such as dose reduction or discontinuation of the treatment should be taken.	Xanthine derivatives potentiate adrenoreceptor stimulating action of this drug, possibly resulting in a decrease in serum potassium and aggravating cardiovascular adverse reactions. The mechanism responsible for induction of hypokalemia is not known.
Corticosteroids (e.g., betamethasone, prednisolone, and hydrocortisone sodium succinate) and Diuretics (e.g., furosemide)	The combined use of this drug with corticosteroids and diuretics may cause a decrease in serum potassium levels, resulting in arrhythmias. If any of these abnormalities are observed, appropriate measures such as dose reduction or discontinuation of the treatment should be taken.	Corticosteroids and diuretics augment the excretion of potassium from renal tubules, possibly resulting in an excessive decrease in serum potassium levels.

PHYSICOCHEMISTRY

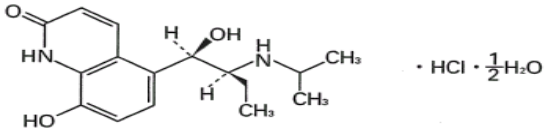
Nonproprietary name:

Procaterol hydrochloride

Chemical name:

8-Hydroxy-5-[(1*RS*,2*SR*)-1-hydroxy-2-isopropylaminobutyl]-quinolin-2(1*H*)-one monohydrochloride hemihydrate

Structural formula:



$\cdot HCl \cdot \frac{1}{2}H_2O$

and enantiomer

Molecular formula:

$C_{16}H_{22}N_2O_3 \cdot HCl \cdot 1/2H_2O$

Molecular weight:

335.83

Description:

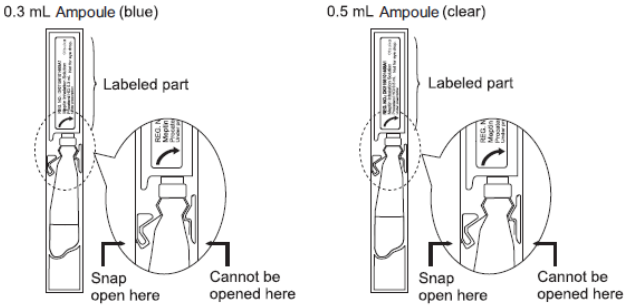
Procaterol hydrochloride occurs as white to pale yellow-white crystals or crystalline powder. It is soluble in water, formic acid and methanol, slightly soluble in ethanol (95), and practically insoluble in diethyl ether. The pH of its aqueous solution (1→100) is 4.0-5.0. Its aqueous solution (1→20) shows no optical rotation. It gradually changes in color when exposed to light.

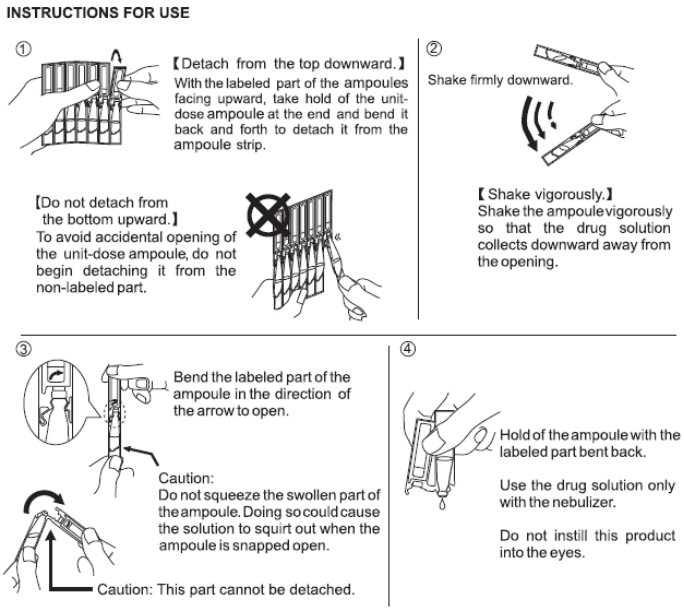
Melting point: Approx. 195°C (decomposition)

PRECAUTIONS FOR HANDLING

MEPTIN® Inhalation 0.3 and 0.5 mL Unit-doses

- This product is for inhalation use only, and must never be instilled into the eyes.
  (To prevent incorrect use, the ampoule is designed so that the labeled part remains attached when the ampoule is snapped open.)
- Open each unit dose ampoule only immediately before use, and use the entire contents of the ampoule at one time
- Store the product protected from direct sunlight, such as in a medicine envelope
- Keep out of the reach of children
- Discard any drug solution remaining in the nebulizer
- Always gargle after inhalation.





STORAGE

Store below 25 °C, avoid from light.

HARUS DENGAN RESEP DOKTER

PACKAGING

MEPTIN® Inhalation Solution 0.3 mL Unit: 0.3 mL × 28

No. Reg.: DKI1156101468A1

MEPTIN® Inhalation Solution 0.5 mL Unit: 0.5 mL × 28

No. Reg.: DKI1156101468A1

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For Otsuka Pharmaceutical Co., Ltd.

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Malang, 65216
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