Meptin® Tablets

< Procaterol Hydrochloride Hydrate Tablets >

COMPOSITION

1. Composition

Each Meptin tablets contains 50 μg of procaterol hydrochloride hydrate.

2. Product Description

Meptin tablets are white compressed tablet, scored on one side.

Appearance	Diameter (mm)	Thickness (mm)	Weight (mg)	Code
OG 21	6	2.1	approx. 80	OG21

INDICATIONS

For the treatment of dyspnea caused by bronchial asthma, chronic bronchitis, and pulmonary emphysema.

CONTRAINDICATIONS

(Meptin Tablets are 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 50 μg (one tablet) once before bed or twice daily (in the morning and before bed) by the oral route. The dosage should be increased or decreased depending upon patients age, condition.

PHARMACOLOGY

1. Bronchodilatory Action

The bronchodilative action of procaterol hydrochloride hydrate was comparable to or more potent than that of isoproterenol and more potent than that of salbutamol sulfate and orciprenaline sulfate, as determined by inhibition on increased pulmonary resistance in dogs, cats, and guinea pigs.

2. Duration of Bronchodilatory Action

Procaterol hydrochloride hydrate had a longer duration of action than isoproterenol, trimetoquinol, orciprenaline sulfate, and salbutamol sulfate in dogs, cats, and guinea pigs.

3. Selectivity for ß$_2$-Adenergic Receptors (Organ Selectivity)

The selectivity of procaterol hydrochloride hydrate for ß$_2$-adrenergic receptors in the respiratory system was greater than that for such receptors in the cardiovascular system, as compared to isoproterenol, trimetoquinol, orciprenaline sulfate, and salbutamol sulfate in dogs, cats, and guinea pigs.

4. Anti-allergic Action

Procaterol hydrochloride hydrate exhibited a definite anti-allergic action by inhibiting antibody-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 antibody inhalation in bronchial asthma patients, as compared to isoproterenol, trimetoquinol, orciprenaline sulfate, and salbutamol sulfate. The drug also inhibited allergen-induced delayed-type and immediate-type bronchial responses.

5. Effects on Airway Secretion

Procaterol hydrochloride hydrate accelerated ciliary activity in airways of pigeons.

6. Inhibitory Effect on Exercise-Induced Asthma Episodes

The results of treadmill or ergometer exercise or methacholine loading tests suggest that procaterol hydrochloride hydrate suppresses exercise-induced asthma attacks in patients with bronchial asthma.

7. Effect on Airway Hypersensitivity

Procaterol hydrochloride hydrate inhibited airway hypersensitivity accelerated by the inoculation of influenza virus C in dogs.

8. Effect on Vascular Permeability Increase

Procaterol hydrochloride hydrate inhibited vascular permeability increase and edema formation in dorsal subcutaneous air pouches induced by various inflammatory chemical agents in rats.

Its potency was similar to that of isoproterenol. Procaterol hydrochloride hydrate also inhibited pulmonary edema induced by histamin inhalation in guinea pigs, with greater potency than salbutamol sulfate.

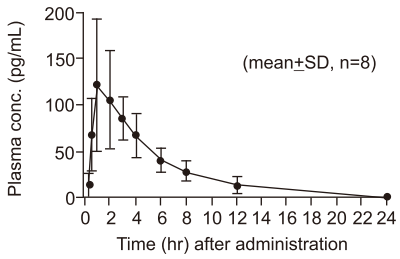
9. Effect on Cough

Procaterol hydrochloride hydrate inhibited cough in acute bronchitis induces by the inhalation of substance P.

PHARMACOKINETICS

1. Plasma Concentrations

When Meptin Tablets 50 μg were administered orally to 8 healthy male subjects as single doses of 50μg/subjects as procaterol hydrochloride hydrate, the following plasma concentration curves and pharmacokinetic parameters were obtained.



Plasma kinetic data

t_{max} (hr)	C_{max} (pg/mL)	$t_{1/2}$ (hr)	AUC $_{\infty}$ (pg·hr/mL)
1.4 ± 0.82	136.4 ± 62.9	3.83 ± 0.93	690.2 ± 262.9

2. Metabolism and Excretion

Following single oral administration of Meptin Tablets 50 μg at a dose of 50μg/subject as procaterol hydrochloride hydrate, 15.7% of the administered dose was excreted as unchanged compound in the urine within 24 hours postdosing, and 23.6% was excreted as a glucuronide metabolite. Desisopropyl procaterol was also detected as a metabolite in the urine, accounting for 0.48 % of the administered dose. It is believed that the main metabolic pathway in humans is glucuronide conjugation.

3. Metabolizing enzyme

CYP3A4 is the main enzyme involved in the formation of desisopropyl procaterol (*in vitro*).

PRECAUTIONS

1. Careful Administration (Meptin Tablets 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 during pregnancy or suspected pregnancy (See Use during Pregnancy, Delivery or Lactation section.)

2. Important Precautions

(1) The mainstay of long term management of bronchial asthma is anti-inflammatory agents such as inhaled corticosteroids. Meptin tablets should therefore be used only as additional therapy for patients whose symptoms are not adequately controlled by inhaled corticosteroids or other asthma medications, or whose disease severity clearly warrants initiation of treatment with Meptin tablets.

As Meptin tablets are not a substitute for inhaled corticosteroids and other anti-inflammatory agents, the patient or their guardian or other legally authorized person should be instructed not to reduce the dosage of inhaled corticosteroid or to stop use of inhaled corticosteroids and switch to monotherapy with Meptin tablets unless specifically instructed to do so by their physician, even if they have felt symptomatic improvement with the use of Meptin tablets.

(2) During the long-term management of bronchial asthma with Meptin tablets, the patient may develop acute asthma episodes. The patient or their guardian or other legally authorized person should therefore be instructed to use adequate drugs other than Meptin tablets, such as short-acting inhaled β_2 stimulants, if acute asthma episodes occur during treatment with Meptin tablets.

In addition, if the use of such drugs becomes more frequent or sufficient therapeutic effect is not observed with the initial dose of the drugs, the patient's asthma may not be adequately controlled. The patient or their guardian or other legally authorized person should be instructed to consult a physician as soon as possible and receive adequate medication in such cases. In addition, as such conditions may be life-threatening, anti-inflammatory therapy should be consolidated by adequate measures, such as increasing the dosage of inhaled corticosteroids.

(3) If the desired therapeutic effect of Meptin tablets cannot be achieved at the recommended dose, the drug should be discontinued.

(4) Continuous administration 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.

3. Use in the Elderly

Dosage adjustment or other appropriate measures should be considered when prescribing Meptin tablets 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 hydrate is excreted in the breast milk.)

5. Pediatric Use
The safety of Meptin Tablets in low birth weight infants, newborns, suckling infants, infants, and children has not been established. (There is no clinical experience in low birth weight infants, newborns, and suckling infants. Clinical experience in infants and children is insufficient.)

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. Other Precautions
(1) Tissue damage in cardiac muscle was noted at 30 mg/kg/day in 14-week repeated dose toxicity study in rats and at 10 mg/kg/day or higher in a 26-week repeated dose toxicity study in rats. The damage was also observed in dog studies. However, the damage has been reported with other β_2-adrenergic agonists in both rats and dogs.
(2) Dietary administration of procaterol hydrochloride hydrate for 104 weeks was reported to cause mesovarian leiomyoma in SD rats. However, the tumor is rat species specific and tends to develop during the long-term administration of β_2- adrenergic stimulants.

8. Overdosage
Overdosage with Meptin Tablets has been associated with tachycardia, tachycardiac arrhythmia, hypotension, nervousness, tremor, hypokalemia, and hyperglycemia. In the event any overdosage-related abnormalities are observed. Meptin Tablets 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, ß-blockers such as propranolol hydrochloride may be effective, but administration of these drugs to asthma patients should be performed with care because ß-blockers may increase airway resistance in these patients.

ADVERSE REACTIONS
In clinical trials involving 22,757 subjects, a total of 644 patients (2.83%) showed adverse reactions including abnormal laboratory values (Figures represent total cases of reported at the time of approval of the initial application, completion of reexamination, and approval of an additional indication for the oral formulations: MEPTIN Tablets, MEPTIN-Mini Tablets, MEPTIN Granules, and MEPTIN Syrup). The following summary of data includes adverse reactions reported after marketing without data on the incidence.

(1) Clinically significant adverse reactions (*incidence unknown)
1) Shock, anaphylaxis: Shock or anaphylaxis 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 hydrate. If xanthine derivatives, corticosteroids, or diuretics are coadministered with this drug in 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 in 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	Facial Flushing, etc	Supraventricular extrasystoles, supraventricular tachycardia, ventricular extrasystoles, atrial fibrilation, etc
Psychoneurologic	Tremor, headache	Dizziness, insomnia numbness of limbs, etc.	Finger spasticity, muscle cramps, muscular spasm, and nervousness
Gastrointestinal	Nausea, vomiting.	Dry mouth, gastric discomfort, etc.	
Hypersensitivity (note)	Skin rash, etc		Pruritus
Hepatic			Increases in AST (GOT), ALT (GPT), and LDH levels and other signs of hepatic dysfunction
Other		Generalized malaize, weakness, nasal obstruction, and tinnitus	Decrease in serum potassium levels, increase of blood sugar level

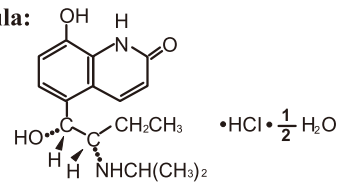
Note 1) If symptoms of hypersensitivity occur, the drug should be discontinued immediately
* The incidences of adverse reactions reported voluntarily after marketing or those reported outside Japan are not known.

DRUG INTERACTIONS
Precautions for coadministration (Meptin Tablets should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Catecholamines (e.g. adrenaline and isoproterenol)	The combined use of this drug with catecholamines may cause arrhythmias or, in some cases, cardiac arrest.	Adrenaline, isoproterenol and other catecholamines potentiate adrenoreceptor stimulating action of this drug. possibly resulting in the induction of arrhythmias.
Xanthine derivatives (e.g. theophylline aminophylline hydrate and diprophylline)	The combined use of this drug with xanthine derivatives may aggravate hypokalemia and cardiovascular adverse reactions (e.g. tachycardia, arrhythmias) due to ß-adrenergic stimulation. If any of these abnormalities are observed, the dose should be reduced or treatment should be discontinued immediately	Xanthine derivatives potentiate adrenoreceptor stimulating action of this drug, possibly resulting in a decrease in serum potassium levels 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 hydrate (JAN)
Chemical name:
8-Hydroxy-5-{(1*RS*,2*SR*)-1-hydroxy-2-[(1-methylethyl)amino]butyl}quinolin-2(1*H*)-one monohydrochloride hemihydrate

Structural formula:



and enantiomer

Molecular formula: $C_{16}H_{22}N_2O_3 \cdot HCl \cdot 1/2H_2O$
Molecular weight: 335.83

STORAGE
Store below 30°C, protect from moisture and light

PACKAGING
Meptin tablets
Container of 10 Alu-alu blisters, each alu-alu blister consist of 10 tablets

REG. NO.: DKL8118700110A1

HARUS DENGAN RESEP DOKTER

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