Natrapharm

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Procaterol Hydrochloride

Brezu® Syrup

5mcg/mL
Bronchodilator

DESCRIPTION

1. Composition

Brand Name	Active Ingredients	Inactive Ingredients
Brezu Syrup 5 mcg/mL	One mL contains 5 mcg of prcaterol hydrochloride	Ethyl Paraben (Ethyl parahydroxybenzoate), butyl paraben (butyl parahydroxybenzoate), sodium benzoate, orange essence, sucrose, Alcohol (ethyl alcohol), citric acid anhydrous, sodium citrate, and purified water

2. Product Description

Procaterol Hydrochloride (Brezu®) Syrup is a colorless, clear, and slightly viscous liquid. It has an orange fragrance and a sweet taste. pH: 3.5 -4.5.

INDICATIONS

Relief of dyspnea and other symptoms caused by respiratory obstructive disturbance in the following disease: bronchial asthma, chronic bronchitis, and pulmonary emphysema. For the treatment of acute bronchitis.

DOSAGE AND ADMINSTRATION

The usual adult dosage is 50 mcg of procaterol hydrochloride (10 mL of Procaterol HCl (Brezu®) Syrup 5 mcg/mL) once daily (at bed time) or twice daily (in the morning and at bed time) by the oral route. The dose for children 6 years of age or older is 25 mcg of procaterol hydrochloride (5 mL of Procaterol hydrochloride) (Brezu®) Syrup once daily (at bed time) or twice daily (in the morning and at bed time) by the oral route. The dose for children younger than 6 years of age 1.25 mcg of procaterol hydrochloride (0.25 mL of Procaterol hydrochloride (Brezu®) Syrup) per kg body weight twice daily (in the morning and at bed time) or three times daily (in the morning, in the early afternoon and at bed time) by the oral route. The dosage may be adjusted according to the patient's age and severity of symptoms.

Reference: Conversion table for a single dose of Procaterol hydrochloride (Brezu®) syrup 5mcg/ml for children younger than 6 years old.

B.W.	Dose	B.W.	Dose	B.W.	Dose
4 kg	1.0 mL	10 kg	2.5 mL	16 kg	4.0 mL
6 kg	1.5 mL	12 kg	3.0 mL	18 kg	4.5 mL
8 kg	2.0 mL	14 kg	3.5 mL	20 kg	5.0 mL

B.W. - Body Weight

PRECAUTIONS

1. Careful Administration (Procaterol Hydrochloride (Brezu®) Syrup should be administered with care in the following patients.)

(a) Patients with hyperthyroidism, where the disease may be exacerbated.
(b) Patients with hypertension, where blood pressure may further increase.
(c) Patients with heart disease (Palpitation, arrhythmia, exacerbation of heart disease and other symptoms may occur)
(d) Patients with diabetes mellitus, where the disease may be exacerbated.
(e) Patients during pregnancy or suspected of being pregnant (See **"6. Use during Pregnancy, Delivery, or Lactation".)**

2. Important Precautions

(1) The mainstay of long-term management of bronchial asthma is anti-inflammatory agents such as inhaled corticosteroids. Procaterol Hydrohloride (Brezu®) Syrup 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 Procaterol Hydrochloride (Brezu®) Syrup. As Procaterol Hydrochloride (Brezu®) Syrup is 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 corticosteroids or to stop use of inhaled corticosteroids and switch to monotherapy with Procaterol Hydrochloride (Brezu®) Syrup unless specifically instructed to do so by their physician, even if they have felt symptomatic improvement with the use of Procaterol Hydrochloride (Brezu®) Syrup
(2) During thte long-term management of bronchial asthma, chronic bronchitis and Pulmonary emphysema with Procaterol Hydrochloride (Brezu®) Syrup, 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 Procaterol Hydrochloride (Brezu®) Syrup, such as short-acting inhaled $ß_2$ stimulants, if acute asthma episodes occur during treatment with Procaterol Hydrochloride (Brezu®) Syrup. 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 Procaterol Hydrochloride (Brezu®) Syrup 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 dosage of this drug.

3. Drug Interactions

(1) For coadministration (Procaterol Hydrochloride (Brezu®) Syrup should be administered with care when coadministered with the following drugs.)

Drugs	Signs, symptoms, and treatment	Mechanism and risk factors
Cathecolamines (e.g. adrenalines and isoprenaline)	The combined use of this drug with catecholamines may cause arrhythmias or, in some cases, cardiac arrest.	Adrenaline, isoprenaline, and other cathecolamines potentiate the adrenoceptor-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 ß-adrenergic stimulation.	Xanthine derivatives potentiate adrenoceptor-stimulating action of this drug, possibly resulting in a decrease in serum potassium levels and aggravating cardiovascular adverse
	If any of these abnormalities are observed, appropriate measures, such as dose reduction or discon-tinuation of the treatment, should be taken.	reactions. The mechanism responsible for the 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 discon-tinuation of the treatment, should be taken.	Corticosteroids and diuretics augment the excretion of potassium from the renal tubules, possibly resulting in an excessive decrease in serum potassium levels.

4. Adverse Reactions (Japanese Data)

In clinical trials involving 22,757 subjects, a total of 644 patients (2.83%) showed adverse reactions including abnormal laboratory values. The following summary of data includes adverse reactions reported after marketing without incidence.

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

i. **Shock, Anaphylactoid reaction:** Shock or anaphylactoid reaction may occur. Patient should therefore be closely monitored. If abnormal findings are observed, the drug should be discontinued and appropriate measures be taken.
ii. **Significant decreases in serum potassium levels** have been reported in patients receiving procaterol hydrochloride.
If **xanthine derivatives, corticosteroids, or diuretics are coadminis tered 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 $ß_2$-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

(b) Other adverse reactions

	5% > ≥ 0.1%	<0.1%	*incidence unknown
Cardiovascular	Palpitations and tachycardia	Facial flushing, etc.	Supraventricular extrasystoles, supraventricular tachycardia, ventricular extrasystoles, atrial fibrillation, etc.
Psychoneurologic	Tremor and headache	Dizziness, insomnia, numbness of limbs, etc.	Finger spasm, muscle cramps, muscular spasm, and nervousness
Gastrointestinal	Nausea and vomiting	Dry mouth gastric discomfort, etc.	
Hypersentivity (Note)	Skin rash, etc.		Pruritus
Hepatic			Increase in AST (GOT), ALT (GPT), and LDH levels and other signs of hepatic dysfunction
Other		Generalized malaise, weakness, nasal obstruction, and tinnitus	Decrease in serum potassium levels and increase in blood sugar level

(Note) If symptoms of hypersensitivity occur the drug should be discontinued immediately.
* :The incidence rate of adverse reactions reported voluntarily after marketing and those reported outside Japan are not known.

5. Use in the Elderly

Dosage adjustment or other appropriate measures should be considered when prescribing Procaterol Hydrochloride (Brezu®) Syrup to elderly patients, because these patients may be physiologically more sensitive to the drug than younger patients.

6. Use during Pregnancy, Delivery, or Lactation

a. 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.)
b. Nursing should be interrupted before starting treatment with Procaterol Hydrochloride (Brezu®) Syrup (Rat studies showed that procaterol is excreted in breast milk.)

7. Pediatric use

The safety of this drug in low birth weight infants and neonates has not been established. (There is no clinical experience in low birth weight infants and neonates.)

8. 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.

9. Overdosage

Overdosage with Procaterol Hydrochloride Syrup has been associated with tachycardia, tachycardiac arrhythmia, hypotension, nervousness, tremor, hypokalemia, and hyperglycemia and lactic acidosis. In the event any overdosage related abnormalities are observed, Procaterol Hydrochloride (Brezu®) Syrup 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.

10.Precaution Concerning Use

At time of dispensing: Patients should be instructed to keep the drug out of the reach of children to avoid accidental ingestion.

11.0ther Precautions

(1)Tissue damage in cardiac muscle was noted at 30 and 10 mg/kg/day or higher in the subacute and chronic toxicity studies, respectively, using rats. [1,2]) The damage was also observed in dog studies. However, the damage has been reported with other $ß_2$-adrenergic agonists in both rats and dogs.
(2) Dietary administration of procaterol hydrochloride for 104 weeks was reported to cause mesovarian leiomyoma in SD rats. The tumor, however, is rat-specific and tends to develop during long-term use of $ß_2$adrenergic agonists.[3])

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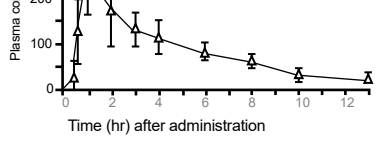
PHARMACOKINETICS

1. Plasma Concentrations[4])

When Procaterol Hydrochloride Syrup was administered orally to 44 healthy male subjects at single doses of 100mcg/subject[Note] as procaterol hydrochloride, in a fasting condition, the following plasma concentration curves and pharmacokinetic parameters were obtained.



Pharmacokinetic parameters of procaterol

	^{t}max (hr)	^{c}max (pg/mL)	$^{t}½$ (hr)	AUC 13hr (pg.hr/mL)
Syrup	1.3 + 0.7	263 ± 104	4.1 ± 1.8	1151 ± 288

(Mean ± SD, n=44)

2. Urinary Excretion[5])

When Procaterol Hydrochloride Syrup was administered orally as single doses of 50 and 100 mcg/subject[Note] as procaterol hydrochloride, 9.93% and 11.65% of the dose were excreted into the urine within 24 hours postdosing, respectively.

3. Cytochrome P450 Isozyme for Hepatic Oxidized Metabolism of Drugs[6])

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

[Note]. The approved dose for a single administration of Procaterol Hydrochloride for adults is 50 mcg.

CLINICAL STUDIES

Procaterol Hydrochloride Syrup was studied in children. The clinical efficacy of the drug by single administration in those with bronchial asthma was 82.9% (34/41), the efficacy by repeated administration in those with bronchial asthma or asthma-like bronchitis was 50.7% (116/229), and the efficacy by repeated administration in those with acute bronchitis was 75.9% (104/137).[7-9])

PHARMACOLOGY

a. Mechanism of Action

Procaterol hydrochloride selectively stimulates $ß_2$-adrenergic receptors of bronchial smooth muscle and develops broncodilative action.

b. Bronchodilative Action[10-14])

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

c. Duration of Bronchodilative Action[10-12])

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

d. Selectivity for $ß_2$-Adrenergic Receptors (Organ Selectivity)[10-13])

The selectivity of procaterol hydrochloride for $ß_2$-adrenergic receptors in the respiratory system was greater than that for such receptors in the cardiovascular system, as compared to isoprenaline, trimetoquinol, orciprenaline, sulfate and salbutamol sulfate, in dogs, cats, and guinea pigs.

e. Anti-allergic Action[15-20])

Procaterol hydrochloride exhibited definite anti-allergic actions by inhibiting antigen-induced increases 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 isoprenaline, trimetoquinol, orciprenaline sulfate, and salbutamol sulfate. The drug also inhibited allergen-induced delayed-type and immediate-type bronchial responses.

f. Effects on Respiratory Tract System[21])

Procaterol hydrochloride accelerated ciliary movement in the airway of pigeons.

g. Effect on Exercise-Induced Asthmatic Attacks[22])

Procaterol hydrochloride suppressed treadmill exercise-induced asthmatic attacks in children with bronchial asthma.

h. Effect on Airway Hypersensitivity[23])

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

i. Effect on Vascular Permeability Increase[24,25])

Procaterol hydrochloride inhibited vascular permeability increase and edema formation in dorsal subcutaneous air pouchs induced by various inflammatory chemical agents in rats. Its potency was similar to that of isoprenaline. Procaterol hydrochloride also inhibited pulmonary edema induced by histamine inhalation in guinea pigs, with greater potency than salbutamol sulfate.

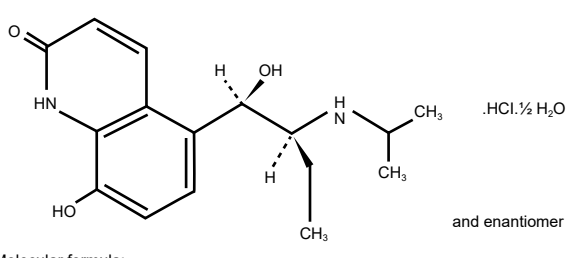
j. Effect on Cough[26])

Procaterol hydrochloride inhibited substance P-induced cough in normal subjects with upper respiratory tract infection.

PHYSICOCHEMISTRY

Nonproprietary name:
Procaterol hydrochloride
Chemical name:
8-Hydrxy-5-{(1*RS*,2*SR*)-1-hydroxy-2-[(1-methylethyl)amino]butyl}
-quinolin-2-(1*H*)-one monohydrochloride hemihydrate.

Structural formula:



Molecular formula:
$C_{16}H_{22}N_2O_3.HCl.½H_2O$
Molecular weight:
335.83
Description:
Procaterol hydrochloride occurs as white to pale white yellowish 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)

PACKAGING

Procaterol hydrochloride (Brezu®) Syrup 5 mcg/mL, bottle of 60 mL

STORAGE AND HANDLING

Store at temperatures not exceeding 25°C. Procaterol hydrochloride (Brezu®) Syrup should be protected from light. Keep out of reach of children.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
FDA Registration No. DRP-5277-01

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

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