Selective β1 Antagonist

Japanese Pharmacopeia **Bisoprolol Fumarate Tablet**

NIKP-Bisoprolol tablet 2.5mg
NIKP-Bisoprolol tablet 5mg

This package insert is continually updated: please read carefully before using a new pack. In case of any question, please contact your physician or pharmacist.

[WARNINGS]

1. **For patients with chronic heart failure, use only under the direction of a physician with adequate experience treating chronic heart failure.**
2. **For patients with chronic heart failure, attention should be paid to worsening of symptoms at the initial administration or when dose amount is increased, and any dosage adjustments should be made with caution. (Refer to "Precautions Regarding Dosage and Administration," "Important Precautions," and "Other Precautions.")**

[CONTRAINDICATIONS (This drug is contraindicated in the following patients.)]

1. Patients with severe bradycardia (significant sinus bradycardia), atrioventricular block (second or third degree), sinoatrial block, sick sinus syndrome [May lead to worsening of symptoms.]
2. Patients with diabetic ketoacidosis and metabolic acidosis [May lead to strengthened suppression of cardiac contractility due to acidosis.]
3. Patients with cardiogenic shock [May suppress heart function and lead to worsening of symptoms.]
4. Patients with right heart failure due to pulmonary hypertension [May suppress heart function and lead to worsening of symptoms.]
5. Patients with heart failure that require intravenous administration of cardiac stimulants or vasodilators [May lead to worsening of symptoms due to the suppressive effect against cardiac contractility]
6. Patients with decompensated heart failure [May lead to worsening of heart failure due to the suppressive effect against cardiac contractility.]
7. Patients with severe peripheral circulatory failure (e.g. gangrene) [May suppress dilation of peripheral blood vessels, leading to worsening of symptoms.]
8. Patients with untreated pheochromocytoma (Refer to "Precautions Regarding Dosage and Administration")
9. Pregnant women or women who may be pregnant (Refer to "Pregnancy, Delivery, or Lactation")
10. Patients who have a history of sensitivity to any of the ingredients of this product.

[DESCRIPTION]

1. Composition

NIKP-Bisoprolol tablet 2.5mg

This product is a "Japanese Pharmacopeia Bisoprolol Fumarate Tablet", and contains 2.5mg of bisoprolol fumarate in each tablet.

This product contains lactose, hydroxypropyl cellulose, and magnesium stearate as inactive ingredients.

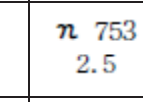
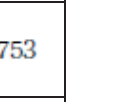
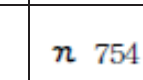
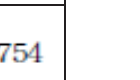
NIKP-Bisoprolol tablet 5mg

This product is a "Japanese Pharmacopeia Bisoprolol Fumarate Tablet", and contains 5mg of bisoprolol fumarate in each tablet.

This product contains lactose, hydroxypropyl cellulose, and magnesium stearate as inactive ingredients.

2. Product description

NIKP-Bisoprolol tablet 2.5mg and NIKP-Bisoprolol tablet 5mg are white uncoated tablets.

Brand name	Appearance Weight (mg)	Appearance Diameter (mm)	Appearance Thickness (mm)	Identification code (on tablet/capsule)	Identification code (on package)
NIKP-Bisoprolol tablet 2.5mg	 90	 6.0	 2.9		
NIKP-Bisoprolol tablet 5mg	 100	 6.5	 3.0		

[INDICATIONS]

- Hypertension
- Angina pectoris
- Adjunct to standard therapy in chronic heart failure

[DOSAGE AND ADMINISTRATION]

1. Hypertension and angina pectoris

The usual adult oral dose is 5mg to 10mg of bisoprolol fumarate once daily. This may be adjusted depending on patient age or symptoms.

2. Adjunct to standard therapy in chronic heart failure

The initial oral dose of bisoprolol fumarate is 1.25*mg once daily. If tolerated, the dose should be doubled after 1 week, and then increased gradually at 1 to 4 weeks intervals to the maximum dose tolerated. The maximum dose should not be exceeding 10mg once daily.

***Other product needs to be chosen for the given strength.**

<Precautions Regarding Dosage and Administration>

1. **For Patients with pheochromocytoma**, administration of this drug in a single dose may lead to a sudden rise in blood pressure. This drug should be administered after initial treatment with alpha blockers and should be used in combination with alpha blockers.
2. Patients with essential hypertension or angina pectoralis combined with chronic heart failure should refer to "Dosage and Administration" regarding chronic heart failure.
3. **Adjunct to standard therapy for chronic heart failure**

1) For administration to patients with chronic heart failure, **the initial dosage must start at 1.25*mg or less once daily, and the maintenance dosage must be set individually for each patient** based on tolerability. (Refer to "Other Precautions")
*Other products need to be chosen for the given strength.
2) **When initial administration or increase in dose** of this product are conducted, **close monitoring must be performed and tolerability should be checked** because worsening of heart failure, edema, weight gain, dizziness, hypotension, bradycardia, fluctuations in blood sugar, and worsened kidney function may occur.
3) In order to avoid worsening of heart failure or retention of fluid (edema, weight gain, etc.) during initial administration or when increasing the dose amount of this drug, **adequate treatment for fluid retention should be performed before administering** this drug. If heart failure or worsening of fluid retention (edema, weight gain, etc.) occurred and improvement is not seen with increased doses of diuretics, dosage amount of this drug is to be decreased or discontinued. If symptoms such as hypotension, dizziness, etc., are observed and improvement is not seen by decreasing dose amount of angiotensin-converting enzyme inhibitors or diuretics, the dosage amount of this drug is to be decreased. If severe bradycardia occurs, the dosage amount of this drug is to be decreased. Furthermore, the dosage amount of this drug should not be increased until these symptoms have stabilized.
4) When administration of this drug is discontinued abruptly, heart failure may worsen. **Discontinuation of this drug** should not be performed suddenly; in principle, the dose amount should be **gradually decreased and then administration should be discontinued**.
5) **When readministering the drug after a drug withdrawal of 2 weeks or longer**, in accordance with "Dosage and Administration," **administration should start from a low dose and gradually increased in dosage**.

[PRECAUTIONS]

1. Careful administration (NIKP-Bisoprolol tablet 2.5mg and NIKP-Bisoprolol tablet 5mg should be administered with care in the following patients.)

(1) Patients at risk of bronchial asthma and bronchial spasms [May constrict bronchial tubes and cause onset of symptoms.]
(2) Patients with idiopathic hypoglycemia, poorly controlled diabetes, long-term fasting [Attention should be paid to blood sugar levels because may mask sympathetic system responses, such as tachycardia, etc., which are prodromal symptoms of low blood sugar.]
(3) Patients with thyrotoxicosis [May mask symptoms of poisoning, such as tachycardia, etc. (Refer to "Important Precautions")]
(4) Patients with severe hepatic or renal dysfunction [May delay metabolism/excretion of the drug and increase the effects.]
(5) Patients with peripheral circulatory failure (Raynaud's syndrome, intermittent claudication, etc.) [May suppress dilation of peripheral blood vessels and cause symptoms to worsen.]
(6) Patients with bradycardia, atrioventricular block (first degree) [May suppress cardiac conduction system of the heart and cause symptoms to worsen.]
(7) Patients with extremely low blood pressure [May risk an even lower drop in blood pressure.]
(8) Patients with variant angina [May cause symptoms to worsen.]
(9) Patients with psoriasis or a history of psoriasis [May trigger or worsen symptoms.]
(10) Elderly patients (Refer to "Elderly")

2. Important Precautions

(1) For **long-term administration, heart function tests** (pulse rate, blood pressure, ECG, X-ray, etc.) should be performed regularly. If symptoms of **bradycardia** or **hypotension** occur, administration should be discontinued or the dosage amount decreased. Further, atropine should be used when necessary. Attention should be paid to hepatic and renal function, hemogram, etc.
(2) When **abruptly discontinuing administration to patients with angina pectoris** who are currently using similar compounds (propranolol hydrochloride), there are cases that have been reported where symptoms worsened or there was onset of myocardial infarction when withdrawal from the drug is necessary, it should be done **gradually** and with careful monitoring. The patient should be warned not to stop taking the drug without the instruction of a doctor. For applications other than angina pectoris, such as irregular pulse, and especially with elderly patients, an equivalent amount of care should be taken.
(3) **When abruptly discontinuing administration to patients with thyrotoxicosis**, symptoms may worsen, and as such, when withdrawal from the drug is necessary, it should be done **gradually** and with careful monitoring.
(4) **No administration within 48 hours prior to surgery** is advisable.
(5) Dizziness or light-headedness may occur, patients who are administered this drug (especially in early stages) should be aware of the **dangers inherent in operating machinery, such as when driving a vehicle**.
(6) **For chronic heart failure**
- For administration to patients with chronic heart failure, it is advisable to **have the patient hospitalized when starting administration or increasing the dose**.
- **For patients with severe chronic heart failure who administrate the drug, careful management is necessary because the patient should be hospitalized when starting administration or increasing dose amount**.

3. Drug Interactions

Precautions for coadministration (NIKP-Bisoprolol tablet 2.5mg and NIKP-Bisoprolol tablet 5mg should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs with suppressive effect on the sympathetic nervous system Reserpine, etc.	May lead to excessive suppression of sympathetic nervous system (bradycardia, hypotension, etc.). If any abnormalities are observed, the dosage should be decreased or administration should be discontinued for both drugs.	Increasing additive affect (effect of sympathetic nervous system depression).
Hypoglycemic drugs Insulin, tolbutamide, etc.	May increase hypoglycemic effects. May also mask symptoms of low blood sugar (tachycardia, sweating, etc.) Attention should be paid to blood sugar levels and if any abnormalities are observed, the dosage should be decreased or administration should be discontinued for this drug.	Suppresses glycogen breakdown in the liver through β2blocking. Additionally masks symptoms of low blood pressure caused by adrenaline secretion when blood sugar is low.
Ca antagonists Verapamil hydrochloride, diltiazem hydrochloride, etc.	May lead to bradycardia, atrioventricular block, sinoatrial block, etc. Pulse rate should be checked regularly and ECGs should be taken when necessary, and if any abnormalities are observed, the dosage should be decreased or administration should be discontinued for both drugs.	Increasing additive affect (effect of suppression of heart stimulation generation/ conduction, negative inotropic effects, hypotensive effects). Attention should especially be paid when used in a 3-drug combination with a digitalis preparation.
Digitalis preparations Digoxin, metildigoxin	May lead to bradycardia, atrioventricular block, etc. ECGs should be performed regularly and if any abnormalities are observed, the dosage should be decreased or administration should be discontinued for both drugs.	Increasing additive affect (effect of suppression of heart stimulation generation/ conduction). Attention should be paid when used in a 3-drug combination with Ca antagonists.
Clonidine hydrochloride, guanabenz acetate	May lead to an increase in rebound reaction (sudden increase in blood pressure) after administration of clonidine or guanabenz discontinued. When discontinuing clonidine, perform appropriate measures beforehand, such as discontinuing administration of this product.	If clonidine is discontinued, noradrenaline in the blood increases. When administered with β blockers, stopping clonidine leads to an enhancement of α effects, causing a sudden rise in blood pressure. Similar reaction can be predicted from the action mechanism of guanabenz as well.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Class I antiarrhythmic agents Disopyramide phosphate, procainamide hydrochloride, ajmaline, etc. Class III antiarrhythmic agents Amiodarone hydrochloride	May lead to excessive suppression of heart function (bradycardia, hypotension, etc.). Monitor clinical symptoms, and if any abnormalities are observed, the dosage should be decreased or administration should be discontinued for this product.	Increasing additive effect (effect of sympathetic nervous system depression).
Non-steroidal anti-inflammatory agents Indomethacin, etc.	May decrease the hypotensive action of this product.	Non-steroidal anti-inflammatory agents inhibit the synthesis/release of prostaglandin.
Drugs with hypotensive action Antihypertensive drugs, nitric acid preparations	May enhance hypotensive action. Perform regular measurements of blood pressure and adjust dosages of both drugs.	Increasing additive effect (hypotensive effect).
Fingolimod hydrochloride	Severe bradycardia or atrioventricular block may be observed when combined with Fingolimod hydrochloride at the start of its administration.	Also may cause bradycardia or atrioventricular block.

4. Adverse Reactions

Surveys or studies that demonstrate frequency of adverse reaction have not been conducted.

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

Heart failure, complete atrioventricular block, severe bradycardia, sick sinus syndrome

As heart failure, complete atrioventricular block, severe bradycardia, or sick sinus syndrome may occur, heart function should be examined regularly, and if any of these adverse reactions occur, appropriate measures should be taken, such as decreasing the dose or discontinuing administration.

(2) **Other adverse reactions**

If an adverse reaction occurs, appropriate measures, such as discontinuing administration, should be taken.

	Frequency unknown
Circulatory organ	Bradycardia, increase in heart/lung ratio, atrioventricular block, hypotension, palpitations, atrial fibrillation, premature ventricular contraction, chest pain
Mental and nervous system	Headache/dull headache, dizziness, light-headedness, dizziness when standing up, sleepiness, insomnia, nightmares
Digestive organ	Nausea, vomiting, stomach discomfort, abdominal discomfort, loss of appetite, diarrhea
Liver	Increased AST (GOT), increased ALT(GPT), increased bilirubin, increased LDH, increased Al-P, increased γ-GTP, enlargement of the liver
Kidneys, urinary organs	Increased uric acid, increased creatinine, increased BUN, sugar in urine, frequent urination
Respiratory organ	Difficulty breathing, bronchial spasms
Hypersensitivities	Rash, skin pruritus
Eyes	Blurred vision, decrease in secretion of tears
Other	Malaise, edema, weakness, sense of discomfort, fatigability, coldness in limbs, chills, numbness, increase in serum lipids, increase in CK (CPK), worsening of diabetes

5. Elderly

For elderly patients, attention should be paid to the following, and the drug should be administered carefully while monitoring the patient's condition, e.g., starting from a small dose when beginning administration.

(1) In general, excessive drops in blood pressure are not advisable for elderly patients. [May lead to cerebral infarction, etc.]

(2) Because pulse rate and heart rhythm trouble, such as bradycardia, etc., occur more easily in elderly patients, dosage should be decreased or administration should be discontinued if such symptoms occur.

(3) If withdrawal from the drug is necessary, the dosage should be decreased gradually. (Refer to "Important Precautions").

6. Pregnancy, Delivery or Lactation

(1) The drug should not be administered to pregnant women or women who may be pregnant. [Animal studies (rat) reported fetal toxicity (lethal, growth inhibition) and neonatal toxicity (developmental toxicity, etc.).]

(2) Nursing should be avoided during administration. [Animal studies (rat) reported that bisoprolol fumarate transmitted through.]

7. Children

The safety of NIKP-Bisoprolol tablet 2.5mg and NIKP-Bisoprolol tablet 5mg in children has not been established (no clinical experience).

8. Overdosage

(1) **Symptoms**

Overdosage may result in bradycardia, complete atrioventricular block, heart failure, hypotension, bronchial spasms, etc. These symptoms, however, have also been reported as adverse reactions.

(2) **Treatment**

If overdose occurs, administration of the drug should be discontinued and the drug should be eliminated using stomach pump, etc., as necessary while appropriate measures, such as those shown below, are performed.

1) **Bradycardia, complete atrioventricular block**
Atropine sulfate hydrate, isoprenaline hydrochloride, etc., should be administered or cardiac pacing should be performed.

2) **Rapid worsening of heart failure**
Diuretics, cardiac stimulants, or vasodilators should be administered intravenously.

3) **Hypotension**
Cardiac stimulants, vasopressors, transfusion, etc., should be administered or assisted circulation should be performed.

4) **Bronchial spasms**
Bronchodilators such as isoprenaline hydrochloride, β2 stimulants, or aminophylline hydrate, etc., should be administered.

9. Precautions Concerning Usage

Precautions for dispensing

Patients should be instructed to remove the tablets from the blister package prior to use. (It has been reported that, if the blister is swallowed, its sharp corners may puncture the esophageal mucosa, and resulting in serious complications such as mediastinitis.)

10. Other Precautions

(1) For patients taking β blockers, anaphylactic reactions caused by other drugs may become more severe and treatment with normal amounts of adrenalin may not be effective.

(2) In a placebo-controlled double-blind comparative study on Japanese patients with chronic heart failure using a different dosage adjustment method from the approved method (increasing/decreasing daily doses once daily at levels of 0.625, 1.25, 2.5, or 5mg), for the primary endpoint "death due to cardiovascular trouble or hospitalization due to worsening of heart failure," there were no predominance for bisoprolol fumarate over the placebo [event occurrence rates: bisoprolol fumarate group 13/100 cases, placebo group 14/100 cases, hazard ratio (95% confidence interval) 0.93 (0.44-1.97)]. Among these, there were 12 cases for bisoprolol fumarate and 9 cases for placebo under "hospitalization due to worsening of heart failure," and there was 1 case for bisoprolol fumarate and 5 cases for placebo under "death due to cardiovascular trouble."

[PHARMACOKINETICS]

1. Bioequivalence Study

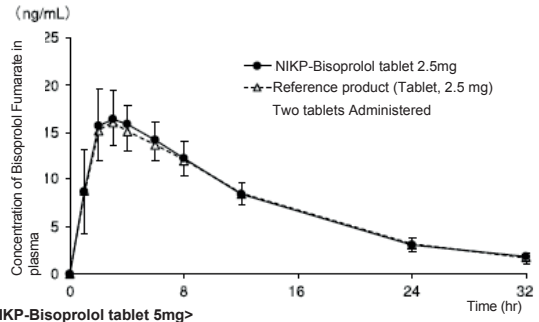
When a single dose of two tablets of NIKP-Bisoprolol tablet 2.5mg or two tablets of the reference product (both tablets contain 5 mg of bisoprolol fumarate) were given to healthy male adults during fasting with a cross-over method, the plasma concentrations of bisoprolol fumarate were measured. In a statistical analysis for the obtained pharmacokinetic parameters (AUC and C_{max}), calculation results of 90% confidence intervals for the parameters were within a range between log (0.8) and log (1.25), demonstrating the bioequivalence of the two formulations.[1)]

Additionally, when one tablet of NIKP-Bisoprolol tablet 2.5mg or one tablet of the reference product (both tablets contain 5mg of bisoprolol fumarate) was administered, similar bioequivalence results of both formations were observed.

<NIKP-Bisoprolol tablet 2.5mg>

	Pharmacokinetic parameters		Reference parameters	
	$AUC_{0\rightarrow32}$ (ng・hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
NIKP-Bisoprolol tablet 2.5mg	235.24± 34.95	17.06± 2.77	3.05± 1.05	8.82± 1.27
Reference product (Tablet, 2.5mg)	230.95± 29.83	16.55± 2.43	3.00± 0.79	8.91± 1.63

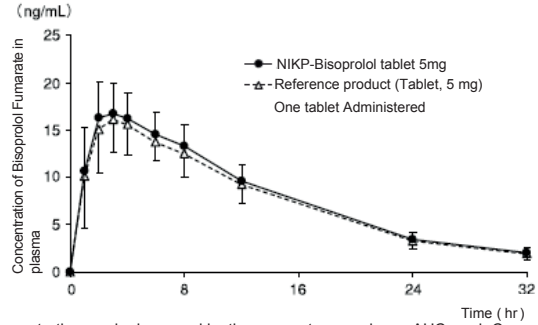
(Administered two tablets, Mean ± S.D., n = 20)



<NIKP-Bisoprolol tablet 5mg>

	Pharmacokinetic parameters		Reference parameters	
	$AUC_{0\rightarrow32}$ (ng・hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
NIKP-Bisoprolol tablet 5mg	255.93± 41.99	17.39± 3.15	2.80± 0.70	8.95± 1.25
Reference product (Tablet, 5mg)	243.65± 43.81	16.96± 3.23	3.00± 1.08	8.97± 1.74

(Administered one tablet, Mean ± S.D., n = 20)



Plasma concentration and pharmacokinetic parameters such as AUC and C_{max} may vary depending on study conditions including selection of subjects, body fluid sampling frequency/sampling time, etc.

2. Dissolution profile

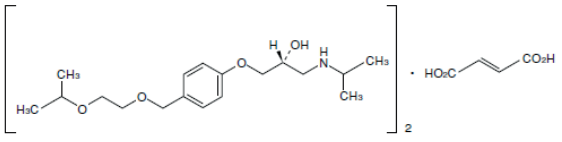
NIKP-Bisoprolol tablet 2.5mg and NIKP-Bisoprolol tablet 5mg have been confirmed to meet the dissolution specification for Bisoprolol Fumarate Tablet stipulated in the Official Monographs of the Japanese Pharmacopeia

[PHYSICOCHEMISTRY]

Nonproprietary name: Bisoprolol Fumarate

Chemical name:

(2*RS*)-1-(4-{[2(1-Methylethoxy)ethoxy]methyl}phenoxy)-3-[(1-methylethyl)amino]propan-2-ol hemifumarate



and enantiomer

Molecular formula: $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$

Molecular weight: 766.96

Description: Bisoprolol Fumarate occurs as white crystals or a white crystalline powder.
It is very soluble in water and in methanol, and freely soluble in ethanol (99.5) and in acetic acid (100).
A solution of Bisoprolol Fumarate (1 in 10) shows no optical rotation.

Melting point: 101-105°C

[PRECAUTIONS FOR HANDLING]

1. Shelf-life

2 years

2. Storage

Store below 25°C
Do not use after expiry date indicated on the outer carton box.

[PACKAGING]

30 tablets (10 tablets x 3 blisters)
100 tablets (10 tablets x 10 blisters)
Not all pack sizes may be marketed.

[NAME OF MANUFACTURER]

Nichi-Iko Pharmaceutical Co., Ltd. Toyama Plant 1

[DATE OF ISSUE]

July 2014

[COUNTRY]

Hong Kong