A-II Antagonist

Japanese Pharmacopoeia Losartan Potassium Tablets

NIKP-Losartan tablet 50mg
NIKP-Losartan tablet 100mg

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.

[CONTRAINDICATIONS (NIKP-Losartan tablet 50mg and 100mg are contraindicated in the following patients.)]

1. Patients with a history of hypersensitivity to any of the ingredients of NIKP-Losartan tablet 50mg or 100mg
2. Pregnant women or women suspected of being pregnant (Refer to "Pregnancy, Delivery or Lactation.")
3. Patients with severe hepatic disorder (Refer to "Careful Administration.")
4. Diabetic patients being administered aliskiren (excluding patients who have extremely poor blood pressure control even when given other antihypertensive treatment) [There are reports of increased risk of non-fatal stroke, renal function disorder, hyperkalemia, and hypotension.] (Refer to "Important Precautions.")

[DESCRIPTION]

1. Composition

NIKP-Losartan tablet 50mg

Listed in the Japanese Pharmacopoeia as "Losartan Potassium Tablets." Each tablet contains 50 mg of losartan potassium. Its excipients are lactose, partly pregelatinized starch, cellulose, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium oxide, and carnauba wax.

NIKP-Losartan tablet 100mg

Listed in the Japanese Pharmacopoeia as "Losartan Potassium Tablets." Each tablet contains 100 mg of losartan potassium. Its excipients are lactose, partly pregelatinized starch, cellulose, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium oxide, and carnauba wax.

2. Product description

NIKP-Losartan tablet 50mg, and NIKP-Losartan tablet 100mg are white, film-coated tablets scored on one side.

Brand name	Appearance Weight (mg)	Appearance Diameter (mm)	Appearance Thickness (mm)	Identification code (on tablet)	Identification code (on package)
NIKP-Losartan tablet 50mg	 156	 7.6	 3.4	*n* 857 50	ⓝ 857
NIKP-Losartan tablet 100mg	 312	 6.9×13.6	 4.3	*n* 858 100	ⓝ 858

[INDICATIONS]

1. Hypertension
2. Diabetic nephropathy in type 2 diabetes, followed with hypertension and proteinuria proteinuria

<Precautions>

For diabetic nephropathy in type 2 diabetes, followed with hypertension and proteinuria

Efficacy and safety of NIKP-Losartan tablet 50mg, and NIKP-Losartan tablet 100mg have not been confirmed for patients that do not have hypertension or proteinuria complications (urinary albumin to creatinine ratio ≥300 mg/g).

[DOSAGE AND ADMINISTRATION]

1. Hypertension:

Normally, the usual adult oral dose of NIKP-Losartan tablet 50mg or 100mg is 25 to 50 mg of losartan potassium once a day. Dose can be suitably increased or decreased in accordance with age or symptoms, but the dose can only be increased up to 100 mg per day.

2. Diabetic nephropathy in type 2 diabetes, followed with hypertension and proteinuria:

Normally, the usual adult oral dose of NIKP-Losartan tablet 50mg or 100mg is 50 mg of losartan potassium once a day. The dose can be increased up to 100 mg per day while observing blood pressure values. However, for patients at risk of an excessive decrease in blood pressure, start administration from 25 mg.

<Precautions Regarding Dosage and Administration>

For diabetic nephropathy in type 2 diabetes, followed with hypertension and proteinuria , if after administration of NIKP-Losartan tablet 50mg, or NIKP-Losartan tablet 100mg, serum creatinine levels increase by 30% (or 1 mg/dL) or greater compared to previous testing levels, and if the propagation rate of renal function disorder is accelerating as assessed by glomerular filtration rate, slope of 1/serum creatinine levels, etc., consideration should be made into lowering the dosage or discontinuing administration.

<Precautions>

1. Careful administration (NIKP-Losartan tablet 50mg and 100mg should be administered with care in the following patients)

(1) Patients with unilateral or bilateral renal artery stenosis (Refer to "Important Precautions.")
(2) Patients with hyperkalemia (Refer to "Important Precautions.")
(3) Patients with severe renal function disorder [Hyperkalemia may occur more easily. As there is also a risk of worsening renal function, if serum creatinine is 2.5 mg/dL or greater, administration should be done carefully, e.g., at a lower dose, etc. (Refer to "Important Precautions.")]
(4) Patients with hepatic function disorder or a history of hepatic function disorder [It has been reported overseas that, compared to healthy adults, patients with mild to moderate alcoholic cirrhosis had a delay in elimination of losartan, and plasma concentrations of losartan and carboxylic acid bodies increased five-fold and two-fold, respectively.]
(5) Patients with cerebrovascular disorders [Excessive decrease in pressure may lead to incomplete cerebral blood flow, possibly making the patient's condition worse.]
(6) Patients with decreased bodily fluids (being administered with antihypertensive diuretic, under severe limitation of salt intake, undergoing hemodialysis) (Refer to "Important Precautions.")

(7) Elderly patients (Refer to “Elderly.”)

2. Important Precautions

(1) For patients with unilateral or bilateral renal artery stenosis, there is a risk of sudden worsening of renal function due to decreased renal blood flow and decreased glomerular filtration pressure, and therefore use should be avoided unless it is judged to be therapeutically unavoidable.

(2) For patients with hyperkalemia, there is a risk that hyperkalemia may become worse, and therefore use should be avoided unless it is judged to be therapeutically unavoidable. Furthermore, for patients for whom elevated serum potassium levels occur more readily due to renal function disorder, poorly controlled diabetes, etc., there is a risk of hyperkalemia, and therefore attention should be paid to serum potassium levels.

(3) When using together with aliskiren, there is a risk of renal function disorder, hyperkalemia, and hypotension, and therefore administration should be done carefully while observing the patient's condition. In case of coadministration with aliskiren in patients with renal function disorder and eGFR below 60 mL/min/1.73 m^2, such usage should be avoided unless it is judged to be therapeutically unavoidable.

(4) The administration of NIKP-Losartan tablet 50mg or 100mg **risks causing transient blood pressure to drop (accompanied by shock symptoms, loss of consciousness, breathing difficulty, etc.). If these symptoms develop, administration should be discontinued and appropriate therapeutic measures should be taken. Blood pressure should be monitored regularly (at the start of administration: every 2 weeks, after stabilization: monthly) during administration of NIKP-Losartan tablet 50mg or 100mg. For the following patients especially, administration should start at a low dose, and if dose is increased, it should be done gradually while carefully observing the patient's condition.**

(i) Patients being administered with antihypertensive diuretic
(ii) Patients under severe limitation of salt intake
(iii)Patients undergoing hemodialysis

(5) Since NIKP-Losartan tablet 50mg and 100mg may induce dizziness or lightheadedness due to its hypotensive effects, patients should be instructed to use with caution when operating hazardous machinery such as working at heights or driving a car.

(6) Administration within the 24 hours before surgery is undesirable.

(7) There have been reports of rare cases of development of hepatitis and other severe hepatic disorders during administration of angiotensin II receptor antagonist, which includes the losartan potassium preparation. Observe the patient carefully, with measures such as hepatic function testing, and take appropriate therapeutic measures, such as discontinuing administration if any abnormality is observed.

(8) Because anemia may occur more easily in patients with diabetic nephropathy in type 2 diabetes, patients should be observed carefully, such as by performing regularly (at the start of administration: every 2 weeks, after stabilization: monthly) blood tests, during administration of NIKP-Losartan tablet 50mg, or NIKP-Losartan tablet 100mg, and if an abnormality is observed, consideration should be paid to a cause of anemia, and appropriate therapeutic measures should be taken.

**(9) Because increased serum potassium and serum creatinine may occur more easily in patients with diabetic nephropathy in type 2 diabetes, patients should undergo regular monitoring (at the start of administration: every 2 weeks, after stabilization: monthly) of serum potassium and serum creatinine levels during administration of NIKP-Losartan tablet 50mg, or NIKP-Losartan tablet 100mg, and careful observation should be given. If an abnormality is observed in serum potassium or serum creatinine levels, appropriate therapeutic measures should be taken. Especially, there are reports that a risk for acute renal failure and hyperkalemia will increase if NIKP-Losartan tablet 50mg or NIKP-Losartan tablet 100mg is used together with an angiotensin- convertase Inhibitor, and as such, care should be taken when using NIKP-Losartan tablet 50mg, or NIKP-Losartan tablet 100mg with an angiotensin-convertase inhibitor.

3. Drug Interactions

NIKP-Losartan tablet 50mg and 100mg are metabolized into active metabolite carboxylate forms, mainly by the drug-metabolizing enzyme cytochrome P450 2C9 (CYP2C9).

Precautions for coadministration (NIKP-Losartan tablet 50mg and 100mg should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Potassium-sparing diuretic Spironolactone, triamterene, etc. Potassium supplement Potassium chloride Angiotensin-convertase inhibitor	Risk of increased serum potassium, hyperkalemia.	Risk of increased potassium retention effect due to coadministration. Special care should be taken for patients with renal function disorder. Furthermore, special care should be taken when using NIKP-Losartan tablet 50mg or 100mg, with both an angiotensin-convertase inhibitor and a potassium-sparing diuretic.
Aliskiren	There is the risk of causing renal function disorder, hyperkalemia, and hypotension. Therefore, careful observation of renal function, serum potassium level, and blood pressure is required. In case of coadministration with aliskiren in patients with renal function disorder and eGFR below 60 mL/min/1.73 m^2, such usage should be avoided unless it is judged to be therapeutically unavoidable.	Coadministration may amplify the inhibitory action of renin-angiotensin system.
** Angiotensin-convertase inhibitor	There is the risk of causing renal function disorder, hyperkalemia, and hypotension. Therefore, careful observation of renal function, serum potassium level, and blood pressure is required.	
NSAIDs Indomethacin, etc.	The antihypertensive effect of NIKP-Losartan tablet 50mg and 100mg may be weakened.	The prostaglandin synthetase inhibitory action may weaken the antihypertensive effect of NIKP-Losartan tablet , 50mg and 100mg.
	In patients with reduced renal function, renal function may be worsened further.	The prostaglandin synthetase inhibitory action is thought to reduce renal blood flow.
Lithium Lithium carbonate	Lithium toxicity has been reported, so blood lithium concentration should be treated with care.	It is thought that the sodium elimination effect of NIKP-Losartan tablet 50mg and 100mg causes accumulation of lithium.

4. Adverse Reactions

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

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

Adverse reactions such as the following may occur, so if these symptoms develop, discontinue administration and take appropriate therapeutic measures.

1) **Anaphylaxis**
Symptoms including discomfort, oral cavity discomfort, sweating, hives, breathing difficulty, generalized flushing, and edema may develop, so careful observation is required.

2) **Angioedema**
Swelling of the face, lips, pharynx, tongue, and elsewhere may manifest as symptoms, so careful observation is required.

3) **Acute hepatitis or fulminant hepatitis**

4) **Renal failure**

5) **Shock, fainting, loss of consciousness**
Shock, fainting followed with blood pressure reduction, and loss of consciousness may occur, so observe the patient carefully, and take appropriate therapeutic measures immediately if chills, vomiting, loss of consciousness, etc. occur. Especially for patients undergoing hemodialysis, under severe limitation of salt intake, or being administered with antihypertensive diuretic, administration should start at a low dose, and if dose is increased, it should be done gradually while observing the patient's condition.

6) **Rhabdomyolysis**
Rhabdomyolysis, characterized by myalgia, torpor, increased CK (CPK), and increased myoglobin in blood and urine, may occur, so if these symptoms develop, discontinue administration and take appropriate therapeutic measures. Also pay attention for the onset of acute renal failure due to rhabdomyolysis.

7) **Hyperkalemia**
Severe hyperkalemia may occur, so observe the patient carefully, and take appropriate therapeutic measures immediately if any abnormality is observed.

8) **Arrhythmia**
Arrhythmias such as premature ventricular contraction and atrial fibrillation may occur, so observe the patient carefully, and take appropriate therapeutic measures immediately if any abnormality is observed.

9) **Pancytopenia, leucopenia, and thrombopenia**
Pancytopenia, leucopenia, and thrombopenia may occur, so observe the patient carefully, and take appropriate therapeutic measures immediately if any abnormality is observed.

10) **Hypoglycemia**
Hypoglycemia may occur (this symptom is common in patients being treated for diabetes), so observe the patient carefully, and discontinue administration and take appropriate therapeutic measures if any of the following symptoms developed: torpor, hunger sensation, cold sweat, hand tremors, reduced concentration, twitching, disturbance of consciousness, etc.

* 11) **Hyponatremia**
Hyponatremia followed with malaise, loss of appetite, nausea, vomiting, twitching, disturbance of consciousness, etc. may occur, so observe the patient carefully, and discontinue administration and take appropriate therapeutic measures immediately if any abnormality is observed.

(2) **Other adverse reactions**

If any of the following symptoms or abnormalities occur, take appropriate therapeutic measures, such as discontinuing administration.

	Frequency unknown
Psychoneurologic	Headache, dizziness, tinnitus, drowsiness, insomnia, anacatesthesia
Cardiovascular	Hypotension, dysrhythmia (tachycardia, etc.), orthostatic hypotension, chest pain, palpitation
** **Gastrointestinal**	Oral ulcer, angular cheilitis, gastric discomfort, gastric ulcer, diarrhea, vomiting/nausea, dry mouth
Hepatic	Hepatic function disorder (increased AST (GOT), increased ALT (GPT), increased LDH, etc.), jaundice
Renal	Increased BUN, increased creatinine
Dermatologic	Erythema multiforme, erythroderma, rash, photosensitivity, erythema, itching, hives
Hematologic	Anemia, reduced red blood cell count, lowered hematocrit, increased eosinophils
** **Others**	Impotence, coughing, fever, burning sensation, dysgeusia, numbness, eye symptoms (blurred vision, discomfort, etc.), malaise, asthenia/ fatigue, edema, arthralgia, muscle twitching, myalgia, increased total cholesterol, inceased CK (CPK), increased blood uric acid level, gynecomastia

5. Elderly

(1) Since physiological functions generally decline with age, attention should be paid to the patient's condition.

(2) Excessive decrease in blood pressure is generally regarded as undesirable in the elderly. (Cerebral infarction, etc. may occur.) Therefore, administration should be done carefully, such as by starting at a low dose, while observing the patient's condition.

(3) Internal pharmacokinetics testing in the elderly has observed higher plasma concentrations of losartan and carboxylate forms than in non-elderly subjects (compared to non-elderly subjects, plasma concentrations of losartan and carboxylate forms were elevated to approximately 2 times and approximately 1.3 times, respectively).

(4) No difference has been observed regarding occurrence of hypotensive effect and adverse reactions between elderly and non-elderly.

6. Pregnancy, Delivery or Lactation

(1) NIKP-Losartan tablet 50mg or 100mg should not be administered to pregnant women or women suspected of being pregnant. If pregnancy is discovered during administration, discontinue administration immediately. [In hypertension patients in the second or third trimester of pregnancy who were administered angiotensin II receptor antagonist, which includes ingredients of losartan potassium preparation, there are reports of oligohydramnios, fetal and newborn death, newborn hypotension, renal failure, multiple organ failure, cranial deformity, limb deformity estimated to be due to oligohydramnios, craniofacial deformity, pulmonary agenesis, etc.]

(2) Administration of NIKP-Losartan tablet 50mg or 100mg should be discontinued during lactation. [Based on animal studies (rats), the drug has been reported to pass into the mother's milk.]

7. Children

The safety of NIKP-Losartan tablet 50mg or 100mg in children has not been established (No clinical experience).

8. 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.)

[Pharmacokinetics]

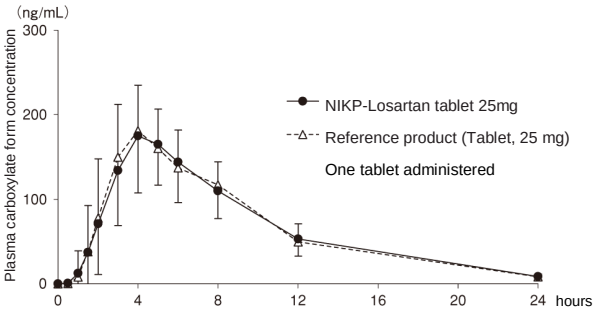
1. Bioequivalence Study

When a single oral dose of one tablet of NIKP-Losartan tablet 25mg or one tablet of the reference product (both tablets contain 25 mg of losartan potassium) was given to healthy male adults during fasting with a cross-over method, the plasma concentration of active metabolite carboxylate form was measured. In a statistical analysis for the obtained pharmacokinetic parameters (AUC and Cmax), calculation results of 90% confidence intervals for the parameters were within a range between log (0.80) and log (1.25), demonstrating the bioequivalence of the two formulations.[1)] Similarly, the results of administration of one tablet of NIKP-Losartan tablet 50mg or one tablet of the reference product (both tablets contain 50 mg of losartan potassium) and one tablet of NIKP-Losartan tablet 100mg or one tablet of the reference product (both tablets contain 100 mg of losartan potassium) showed bioequivalence between the two formulations[1)].

<NIKP-Losartan tablet 25mg>

	Pharmacokinetic parameters		Reference parameters	
	$AUC_{0\rightarrow24}$ (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
NIKP-Losartan tablet 25mg	1574±330	197±50.3	4.5±1.2	4.4±0.3
Reference product (Tablet, 25 mg)	1574±345	206±55.8	4.4±1.4	4.3±0.4

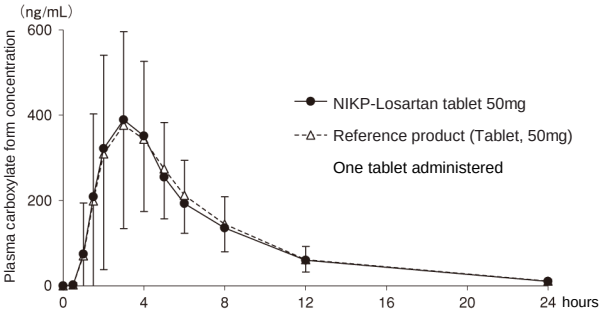
(Administered one tablet, Mean±S.D, n=23)



<NIKP-Losartan tablet 50mg>

	Pharmacokinetic parameters		Reference parameters	
	$AUC_{0\rightarrow24}$ (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
NIKP-Losartan tablet 50mg	2617±1287	424±221	3.4±1.2	4.6±1.1
Reference product (Tablet, 50 mg)	2673±1169	429±228	3.4±1.2	4.6±1.2

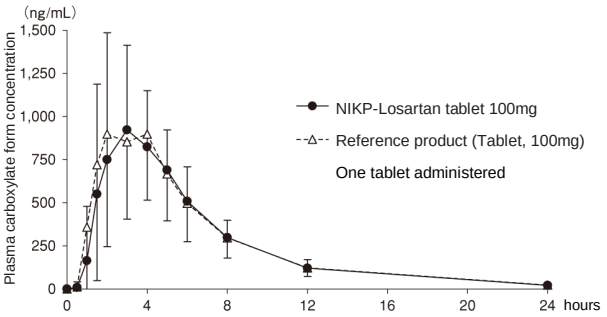
(Administered one tablet, Mean±S.D, n=23)



<NIKP-Losartan tablet 100mg>

	Pharmacokinetic parameters		Reference parameters	
	$AUC_{0\rightarrow24}$ (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
NIKP-Losartan tablet 100mg	6110±2090	1200±449	3.0±1.1	4.3±0.6
Reference product (Tablet, 100 mg)	6396±2066	1270±428	2.9±1.2	4.5±0.6

(Administered one table, Mean±S.D, n=19)



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

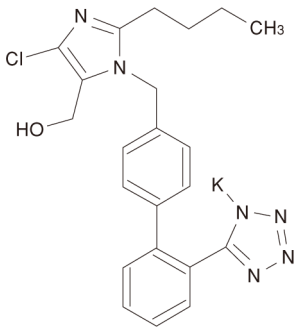
2. Dissolution behavior

NIKP-Losartan tablet 50mg and 100mg have been shown to meet the dissolution regulations for "Losartan Potassium Tablets" set forth in the Official Monographs of the Japanese Pharmacopoeia.[2)]

[PHYSICOCHEMISTRY]

Nonproprietary name: Losartan Potassium

Chemical name: Monopotassium 5{-[4' (-2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazol-1-yl) methyl] biphenyl-2-yl}-1*H*-tetrazol-1-ide



Molecular formula: $C_{22}H_{22}ClKN_6O$

Molecular weight: 461.00

Description: Losartan Potassium occurs as a white crystalline powder. It is very soluble in water, and freely soluble in methanol and in ethanol (99.5).

[PRECAUTIONS FOR HANDLING]

1. Shelf-life

2 years

2. Storage

Store below 25ºC

Do not use after expiry date indicated on the outer carton box.

[PACKAGING]

30 tablets (10 tablets × 3 blisters)

100 tablets (10 tablets × 10 blisters)

Not all pack sizes may be marketed.

[NAME OF MANUFACTURER]

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

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[COUNTRY]

Hong Kong