Persistent ARB/ diuretic compound

Japanese Pharmacopeia **Losartan Potassium and Hydrochlorothiazide Tablets**

NIKP-Losartan HCTZ film-coated tablet 50mg/12.5mg

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.

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

1. Patients with a history of hypersensitivity to any of the ingredients of this drug.
2. Patients with a history of hypersensitivity to thiazide group drugs or similar compounds (such as chlorthalidone and other sulfonamide derivatives)
3. Pregnant women or women suspected of being pregnant (Refer to "Pregnancy, Delivery or Lactation.")
4. Patients with severe hepatic function disorder (Refer to "Careful Administration.")
5. Patients with anuria, and dialysis patients
6. Patients with acute renal failure [This drug could further worsen renal function.]
7. Patients in whom sodium and potassium are clearly depleted in body fluids [This drug could worsen electrolyte imbalances such as hyponatremia and hypokalemia.]
8. The concomitant use of NIKP-Losartan HCTZ film-coated tablet 50mg/12.5mg with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73 m^2).

[DESCRIPTION]

1. Composition

Listed in the Japanese Pharmacopoeia as "Losartan Potassium and Hydrochlorothiazide Tablets". Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide.

Excipients: lactose, cellulose, partly pregelatinized starch, magnesium stearate, hypromellose, hydroxypropyl cellulose, titanium oxide, carnauba wax.

2. Product description

This drug is a white, circular, film-coated tablet.

Brand name	Appearance Weight (mg)	Appearance Diameter (mm)	Appearance Thickness (mm)	Identification code (on tablet)	Identification code (on package)
NIKP-Losartan HCTZ film-coated tablet 50mg/12.5mg	 255	 8.9	 4.1	ロサルヒド LD 日医工	ⓝ 855

[INDICATIONS]

Hypertension

Reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy. (This may not apply to black patients.)

<Precautions>

There are risks including excessive blood pressure reduction. Therefore, this drug should not be the first-choice drug for treatment of hypertension.

[DOSAGE AND ADMINISTRATION]

The adult oral dose of this drug is one tablet (50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide) once a day.

This drug should not be used as the first-choice drug for treatment of hypertension.

<Precautions Regarding Dosage and Administration>

The antihypertensive effect of this drug has not been comparatively investigated against that of drugs other than 50mg of losartan potassium or 12.5 mg of hydrochlorothiazide. In general, the use of this drug should be considered when the effect of 50 mg of losartan potassium is inadequate.

[PRECAUTIONS]

1. Careful administration (This drug 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 renal impairment (Refer to "Important Precautions.")

(3) Patients with abnormal serum potassium values (Refer to "Important Precautions.")

(4) Patients with hepatic function disorder, or past history of hepatic function disorder [It has been reported overseas that when a single oral dose of 50 mg of losartan potassium was administered to patients with light to moderate alcohol-related cirrhosis, the rate of elimination of losartan was slower than in healthy adults, and the plasma concentrations of losartan and carboxylate forms reached approximately 5 times and approximately 2 times, respectively, the levels in healthy adults. Also, hydrochlorothiazide may induce hepatic coma.]

(5) Patients with cerebrovascular disorder [Excessive blood pressure reduction evokes cerebral blood flow insufficiency and may worsen the clinical condition.]

(6) Hypovolemic patients (patients being administered with antihypertensive diuretic, patients under severe limitation of salt intake, patients with insufficient water intake, patients sweating excessively) (Refer to "Important Precautions.")

(7) Patients under limitation of salt intake [There is the risk of causing hyponatremia.]

(8) Patients with severe coronary or cerebral arteriosclerosis [In the event of extreme diuresis, there is the risk of rapid plasma volume reduction and hemoconcentration, inducing thromboembolism.]

(9) Patients with gout or diabetes, or with history of those conditions in their parents or siblings, and patients with hyperuricemia [There is the risk of hyperuricemia and hyperglycemia, leading to worsening or manifestation of gout and diabetes.]

(10) Patients with diarrhea or vomiting [There is the risk of electrolyte imbalance.]

(11) Patients with hypercalcemia or hyperparathyroidism [There is the risk of elevating serum calcium.]

(12) Patients being administered with digitalis agent, adrenal corticosteroid, or ACTH (Refer to "Drug Interactions.")

(13) Patients after sympathectomy [There is the risk that the antihypertensive effect of this drug could be amplified.]

(14) Elderly patients (Refer to "Elderly.")

(15) Nursing infant patients (Refer to "Children.")

2. Important Precautions

(1) This drug contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. Use of this drug should be considered carefully, as there is the risk of manifesting adverse reactions from both losartan potassium and hydrochlorothiazide. (Refer to "Precautions Regarding Dosage and Administration.")

(2) The administration of this drug 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 during the administration of this drug (at the start of administration: every 2 weeks, after stabilization: monthly). In particular, close attention should be given to the condition of the following types of patients:
(i) Patients being administered with antihypertensive diuretic
(ii) Patients under severe limitation of salt intake
(iii) Patients with inadequate water intake
(iv) Patients who sweat excessively

(3) In patients with renal impairment and serum creatinine level at 2.0 mg/dL or above, there is the risk that hydrochlorothiazide may reduce renal blood flow, and that losartan potassium may worsen renal impairment. Therefore, usage in such patients should be avoided unless it is judged to be therapeutically unavoidable.

(4) In patients with decline of renal function and serum creatinine level at 1.5-2.0 mg/dL, there is the risk of elevating the serum creatinine level and serum uric acid level. Therefore, monitor serum creatinine level and serum uric acid level regularly during administration of this drug, and observe the patient carefully.

(5) In patients with unilateral or bilateral renal artery stenosis, there is the risk of sudden worsening of renal function due to reduced renal blood flow or reduced glomerular filtration pressure. Therefore, usage in such patients should be avoided unless it is judged to be therapeutically unavoidable.

(6) Hydrochlorothiazide, which is an ingredient of this drug, is known to cause hypokalemia. In clinical trials conducted in Japan of the administration of 50 mg/12.5 mg of losartan potassium/ hydrochlorothiazide, serum potassium levels tended to decline, and the expression frequency of hypokalemia was even higher than that of hyperkalemia. Therefore, as there is greater concern over the manifestation of hypokalemia, serum potassium levels should be

monitored regularly, with careful observation.

(7) In patients with hyperkalemia, there is the risk that losartan potassium, which is an ingredient of this drug, may worsen hyperkalemia. Therefore, usage in such patients should be avoided unless it is judged to be therapeutically unavoidable. Furthermore, there is the risk of manifestation of hyperkalemia in patients prone to elevated levels of serum potassium due to renal impairment or poorly-controlled diabetes. Therefore, serum potassium levels should be monitored regularly, with careful observation.

(8) Dual blockade of the renin-angiotensin-aldosterone system (RAAS).
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

(9) Hydrochlorothiazide, which is an ingredient of this drug, may cause manifestation of hyperuricemia. Therefore, monitor serum uric acid level regularly during administration of this drug, and observe the patient carefully.

(10) Hydrochlorothiazide, which is an ingredient of this drug, may elevate blood glucose level or cause manifestation of diabetes. Therefore, the patient should be observed carefully.

(11) Dizziness and lightheadedness may appear due to the antihypertensive effect, so caution is required when working in high places, driving a vehicle, or operating other hazardous machinery.

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

(13) 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 ingredients of this drug. 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.

(14) Administration of this drug may cause an intense diuretic effect, so care is required to avoid electrolyte imbalance and dehydration.

(15) Administration before noon is preferable, to avoid nocturnal urination in patients who particularly require nocturnal rest.

3. Drug Interactions

Losartan potassium, which is an ingredient of this drug, is metabolized into carboxylate form, which is an active metabolite, mainly by the drug-metabolizing enzyme cytochrome P450 2C9 (CYP2C9).
Clinical trial data has shown that dual blockade of the RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypertension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.
Hydrochlorothiazide, which is an ingredient of this drug, is excreted in urine with almost no metabolization.

Precautions for coadministration (This drug 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	Serum potassium level elevation may occur.	Coadministration with losartan potassium, which is an ingredient of NIKP-Losartan HCTZ film-coated tablet 50mg/12.5mg, may strengthen the potassium retention action. Particular care is required in patients with renal impairment.
* Aliskiren	There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy. The concomitant use of NIKP-Losartan HCTZ film-coated tablet 50mg/12.5mg with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2.	Coadministration increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure).
* Angiotensin-convertase inhibitor		
Barbituric acid derivatives	Orthostatic hypotension may be increased.	This is due to the central depressant action of these drugs and the antihypertensive effect of hydrochlorothiazide, which is an ingredient of this drug.
Opium alkaloid narcotic		There have been reports of blood pressure reduction due to the administration of large doses of opium alkaloids together with hydrochlorothiazide, which is an ingredient of this drug.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Alcohol	Orthostatic hypotension may be increased	The antihypertensive effect of hydrochlorothiazide, which is an ingredient of this drug, may be strengthened by coadministration with alcohol, which has a vasodilatory effect.
Pressor amine Noradrenaline, adrenaline	The action of pressor amines may be weakened. When using this drug in preoperative patients, take therapeutic measures, such as interrupting administration.	There have been reports of hydrochlorothiazide, which is an ingredient of this drug, reducing the reactivity of pressor amines on vascular walls.
Tubocurarine and substances with similar effects Tubocurarine chloride hydrochloride hydrate, pancuronium bromide	The paralyzing effect of tubocurarine and substances with similar actions may be amplified. When using this drug in preoperative patients, take therapeutic measures, such as interrupting administration.	It is thought that the reduction of the serum potassium level by hydrochlorothiazide, which is an ingredient of this drug, amplifies the neuromuscular blocking effects of these drugs.
* Other drugs with antihypertensive effects β blockers, nitroglycerin, etc.	The antihypertensive effect of this drug could be amplified. Pay attention to dosage adjustment, etc. of antihypertensive drugs.	Cooperative action due to antihypertensive effects with differing mechanisms.
Digitalis agent Digoxin, digitoxin	The effect of digitalis on the heart may be amplified, causing arrhythmia, etc. Pay close attention to serum potassium level.	Reduction of the serum potassium level by hydrochlorothiazide, which is an ingredient of this drug, causes large quantities of digitalis to bond to Na-KATPase in the myocardium, amplifying the force of cardiac contraction and causing arrhythmia. Magnesium reduction has the same effect.
Sodium lactate	Metabolic alkalosis and hypokalemia due to thiazide drugs may be amplified.	The potassium elimination effect of hydrochlorothiazide, which is an ingredient of this drug, may cause hypokalemia and metabolic alkalosis. Coadministration with sodium lactate, which is an alkalization agent, further amplifies this condition.
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 losartan potassium, which is an ingredient of this drug, causes accumulation of lithium.
	Lithium toxicity, such as tremors and digestive organ complaints, may be amplified. Serum lithium concentration should be treated with care.	Hydrochlorothiazide, which is an ingredient of this drug, accelerates the reabsorption of lithium in the kidneys, raising the blood concentration of lithium.
Adrenal corticosteroid ACTH	Hypokalemia may be manifested.	Hydrochlorothiazide, which is an ingredient of this drug, has a potassium elimination effect, as do adrenal corticosteroids and ACTH.
Glycyrrhizinate drugs	Serum potassium levels are more prone to decline.	Glycyrrhizinate drugs may cause pseudoaldosteronism, with hypokalemia as the main symptom. Therefore, the coadministration of hydrochlorothiazide, which is an ingredient of this drug, with glycyrrhizinate drugs may amplify hypokalemia.
Diabetes drugs SU drugs, insulin	The action of diabetes drugs may be severely weakened.	The mechanism is unclear, but the loss of potassium due to hydrochlorothiazide, which is an ingredient of this drug, is thought to reduce the release of insulin by the β cells of the pancreas.
Cholestyramine	The action of thiazide drugs may be weakened.	The adsorption action of cholestyramine inhibits the absorption of hydrochlorothiazide, which is an ingredient of this drug.
NSAIDS Indomethacin, etc.	The antihypertensive effect of this drug could be weakened.	The prostaglandin synthetase inhibitory action may weaken the antihypertensive effect of this drug.
	In patients with reduced renal function, renal function may be worsened further.	The prostaglandin synthetase inhibitory action is thought to reduce renal blood flow.
	The action of thiazide drugs may be weakened.	The prostaglandin synthetase inhibitory action of NSAIDS reduces prostaglandin in the kidneys, leading to accumulation of water and sodium in the body, and resisting the action of hydrochlorothiazide, which is an ingredient of this drug.
Sulfinpyrazone	Thiazide drugs may resist the uric acid elimination action of sulfinpyrazone.	Thiazide diuretics are thought to inhibit the secretion of uric acid in the kidneys and increase uric acid reabsorption, so they may antagonize the uric acid elimination action of sulfinpyrazone.

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, perspiration, 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) **Acute renal failure**
Acute renal failure may occur, so observe the patient carefully, and take appropriate therapeutic measures immediately if any

abnormality is observed.

5) **Shock, fainting, loss of consciousness**
Shock, fainting accompanying 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. Patient condition should be observed with particular care in patients under severe limitation of salt intake and patients being administered with diuretic antihypertensive drugs.

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) **Hypokalemia, hyperkalemia**
Severe hypokalemia and hyperkalemia may occur, and symptoms such as malaise, torpor, and arrhythmia may manifest with abnormal variations in serum potassium level, so observe the patient carefully, and take appropriate therapeutic measures immediately, such as discontinuing administration, 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) **Aplastic anemia, hemolytic anemia**
Severe blood disorders may occur, so observe the patient carefully, and take appropriate therapeutic measures immediately if any abnormality is observed.

11) **Necrotizing vasculitis**

12) **Interstitial lung disease, pulmonary edema**

13) **Aggravation of systemic lupus erythematosus**

14) **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 develop: torpor, hunger sensation, cold sweat, hand tremors, reduced concentration, twitching, disturbance of consciousness, etc.

15) **Hyponatremia**
Hyponatremia accompanied by malaise, loss of appetite, nausea, vomiting, disturbance of consciousness, etc. may occur (this symptom is common in the elderly), so observe the patient carefully, and discontinue administration and take appropriate therapeutic measures immediately if any abnormality is observed.

16) **Acute myopia, angle-closure glaucoma**
Acute myopia (including blurring, decreased visual acuity, etc.) and angle-closure glaucoma may occur, so if sudden decrease in vision, eye pain or similar abnormalities is observed, discontinue administration and instruct the patient to immediately seek treatment from an ophthalmologist.

(2) **Other adverse reactions**
Symptoms and abnormalities such as the following may occur, so if these conditions appear, take appropriate therapeutic measures such as discontinuing administration.

	Frequency unknown
Psychoneurologic	Abnormal perception, dizziness, anacatesthesia, headache, tinnitus, insomnia, drowsiness
Cardiovascular	Hypotension, orthostatic hypotension, dysrhythmia (tachycardia, etc.), chest pain, palpitation
Gastrointestinal	Angular cheilitis, gastric discomfort, gastric ulcer, abdominal colic, pancreatitis, sialadenitis, anorexia, vomiting/nausea, oral ulcer, diarrhea, constipation, dry mouth, abdominal discomfort
Hepatic	Jaundice, hepatic function disorder (increased AST (GOT), increased ALT (GPT), increased LDH, etc.)
Renal	Increased BUN, increased creatinine
Dermatologic	Erythema multiforme, erythroderma, facial flushing, cutaneous lupus erythematosus, rash, photosensitivity, erythema, itching, hives Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.
Hematologic	Increased eosinophils, anemia, reduced red blood cell count, lowered hematocrit, increased white blood cell count, increased red blood cell count, increased hematocrit, increased hemoglobin, increased neutrophil percentage, increased lymphocyte count, reduced lymphocyte count
* **Others**	Fever, xanthopsia, myalgia, coughing, hypomagnesemia, hypochloremic alkalosis, increased serum calcium, impotence, parathyroid disorder accompanied by hypercalcemia, arthralgia, nasal obstruction, gynecomastia, malaise, edema, increased CK (CPK), hyperuricemia, hyperglycemia, pollakiuria, increased CRP, positive urinary staphylococcus, dysgeusia, numbness, eye symptoms (blurred vision, discomfort, etc.), burning sensation, muscle twitching, purpura, neck discomfort, excessive perspiration, breathing difficulty, increased serum lipids, positive for red blood cells in urine, positive for protein in urine, positive for white blood cells in urine, increased BNP, upper respiratory infection

5. Elderly
In the elderly, pay attention to the following points and practice careful administration while observing patient condition.
(1) Excessive decrease in blood pressure is generally regarded as undesirable in the elderly. (Cerebral infarction, etc. could occur.)
(2) Pharmacokinetics testing of single-drug administration of losartan potassium 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).
(3) In the elderly, intense diuresis reduces plasma volume, and may cause dehydration, lightheadedness upon standing, dizziness, fainting, etc. due to hypotension.
(4) Particularly in elderly patients with edema due to heart disease, etc., intense diuresis leads to rapid reduction of plasma volume and hemoconcentration, which may induce cerebral infarction and other thromboembolism.
(5) The elderly are prone to hyponatremia and hypokalemia.

6. Pregnancy, Delivery or Lactation
(1) This drug 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 this drug, 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 this drug should be discontinued during lactation.
(Reference)
Testing in which rats were administered doses ranging from losartan potassium 1 mg/kg/day and hydrochlorothiazide at 0.25 mg/kg/day, up to losartan potassium 50 mg/kg/day and hydrochlorothiazide at 12.5 mg/kg/day, during the perinatal period and lactation period. Results found reduced birth weight and histopathological kidney lesions in the group receiving losartan potassium 50 mg/kg/day and hydrochlorothiazide at 12.5 mg/kg/day. Lacteal transfer of losartan, carboxylate forms, and hydrochlorothiazide was also confirmed. The no observed adverse effect level in infants in this testing was 10 mg/kg/day of losartan potassium and 2.5 mg/kg/day of hydrochlorothiazide.

7. Children
The safety of this drug in low birth weight infants, newborns, nursing infants, and children has not been established. (No clinical experience.)

8. Influence on Clinical Test Results
Caution is required because serum PBI may be reduced in patients with no thyroid disorders.

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.)

[PHARMACOKINETICS]

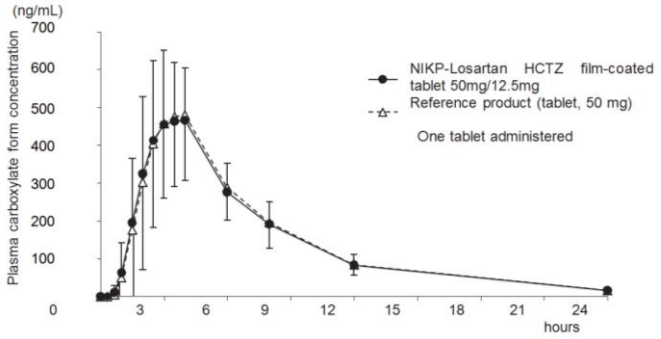
1. Bioequivalence Study
When a single oral dose of one tablet of NIKP-Losartan HCTZ film-coated tablet 50mg/12.5mg or one tablet of the reference product (both tablets contain 50 mg of losartan potassium and 12.5mg of

hydrochlorothiazide) was given to healthy male adults during fasting with a cross-over method, the plasma carboxylate form concentration* and hydrochlorothiazide concentration were 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.
(* Main active metabolites of losartan)

< Losartan potassium >

	Pharmacokinetic parameters		Reference parameters	
	$AUC_{0\rightarrow24}$ (ng･hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
NIKP-Losartan HCTZ film-coated tablet 50mg/12.5mg	3423.42± 882.74	511.88± 158.60	3.30±0.72	4.58±0.40
Reference product (Tablet, 50 mg)	3449.84± 1007.84	533.09± 168.67	3.50±1.31	4.56±0.39

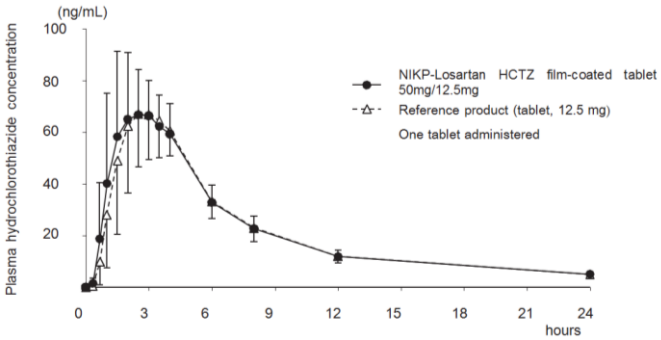
(Administered 50 mg, Mean±S.D., n=23)



<Hydrochlorothiazide>

	Pharmacokinetic parameters		Reference parameters	
	$AUC_{0\rightarrow24}$ (ng･hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
NIKP-Losartan HCTZ film-coated tablet 50mg/12.5mg	515.15± 77.12	82.07± 19.13	2.50±0.99	7.62±1.01
Reference product (Tablet, 12.5 mg)	506.55± 83.16	78.62± 16.08	2.76±0.80	7.62±0.85

(Administered 12.5 mg, Mean±S.D., n=23)



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.

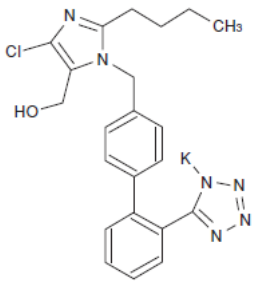
2. Dissolution profile

This drug has been shown to meet the dissolution regulations for losartan potassium and hydrochlorothiazide tablets set forth in the Official Monographs of the Japanese Pharmacopoeia.

[PHYSICOCHEMISTRY]

1. Losartan potassium

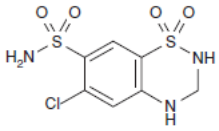
Nonproprietary name: Losartan Potassium
Chemical name: Monopotassium 5-{[4'-(2-butyl-4-chloro-5-hydroxymethyl-1H-imidazol-1-yl) methyl] biphenyl-2-yl}-1H-tetrazol-1-ide



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).

2. Hydrochlorothiazide

Nonproprietary name: Hydrochlorothiazide
Chemical name: 6-Chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide 1, 1-dioxide



Molecular formula: $C_7H_8ClN_3O_4S_2$
Molecular weight: 297. 74
Description: Hydrochlorothiazide occurs as a white crystal or crystalline powder. It is odorless, and has a slightly bitter taste.
It is freely soluble in acetone, sparingly soluble in acetonitrile, very slightly soluble in water and in ethanol (95), and practically insoluble in diethyl ether.
It dissolves in sodium hydroxide test solution.
Melting point: about 267 °C (with decomposition)

[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 × 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

[DATE OF ISSUE]

September 2016

[COUNTRY]

Hong Kong