SELECTIVE ANGIOTENSIN-CONVERTING ENZYME INHIBITOR

TANATRIL® Tablets 5mg

TANATRIL® Tablets 10 mg

(IMIDAPRIL HYDROCHLORIDE)

Caution: Use only pursuant to the prescription or directions of a physician, etc.

Storage
Store at below 30° C. Avoid humidity after opening.

Expiration date
Indicated on the package and container.

CONTRAINDICATIONS (TANATRIL is contraindicated in the following patients.)

1) Patients with a history of hypersensitivity to any of the ingredients of the drug.
2) Patients with a history of angioedema (Angioedema due to drug such as angiotensin converting enzyme (ACE) inhibitors, etc., hereditary angioedema, acquired angioedema, idiopathic angioedema, etc.) [Angioedema associated with dyspnea may occur.]
3) Patients undergoing apheresis by an adsorber using dextran sulfate immobilized cellulose, tryptophan immobilized poly-vinyl alcohol or polyethylene terephthalate [shock may occur.] (See PRECAUTIONS - " Drug Interactions" section.)
4) Patients who undergo hemodialysis with acrylonitrile methallyl sulfonate sodium membrane (AN69®) [Anaphylactoid symptom may occur.] (See PRECAUTIONS - Drug Interactions.)
5) Pregnant women or women who may possibly be pregnant. [See PRECAUTIONS - Use during Pregnancy, Delivery or Lactation.]
6) Patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) being treated with aliskiren fumarate (excluding patients with markedly uncontrolled blood pressure even after antihypertensive treatment with other drugs) [Increased risk for nonfatal stroke, renal impairment, hyperkalemia, and hypotension have been reported.] (See" Important Precautions" section.)
7) Patients receiving sacubitril valsartan sodium hydrate or patients within 36 hours of discontinuation of the drug [Angioedema may occur.] (See “Drug Interactions” section)

DESCRIPTION

Brand name	TANATRIL Tablets 5mg	TANATRIL Tablets 10 mg
Active ingredient (per tablet)	Imidapril hydrochloride	
	5mg per tablet	10 mg per tablet
Dosage form	Plain tablets	
Color	White	
Appearance		
Size (mm)	Diameter: 6.0 mm Thickness: 2.53 mm	Diameter: 6.5 mm Thickness: 2.55 mm
Weight (g)	0.08 g	0.09 g
Identification code	TA 135	TA 136

INDICATIONS
Hypertension. Renal parenchymal hypertension.

DOSAGE AND ADMINISTRATION
The usual adult dosage for oral use is 5mg to 10mg of imidapril hydrochloride once a day. The dosage may be adjusted depending on the patient's age and symptoms. In patients with severe hypertension, hypertension with renal impairment, or renal parenchymal hypertension, the recommended initial dose is 2.5 mg once a day.

< Precautions >
In patients with serious renal impairment whose creatinine clearance levels are less than 30mL/ min. or serum creatinine levels are greater than 3 mg/dL, the drug should be administered with care; consider decreasing the usual dosage to the half or prolonging the time interval between administrations. [Excessive hypotension or further decrease in renal function may occur due to decrease in urinary excretion rate.] (See PRECAUTIONS- Careful Administration and PHARMACOKINETIC.)

PRECAUTIONS
1. Careful Administration (TANATRIL should be administered with care in the following patients.)
1) Patients with bilateral or unilateral renal arterial stenosis. [See " Important Precautions" section.]
2) Patients with Hyperkalemia [See "Important Precautions" section.]
3) Patients with renal impairment. [See <Precautions related to DOSAGE AND ADMINISTRATION> and “Clinically significant adverse reactions” sections.]
4) Patients with cerebrovascular disorders. [Excessive hypotension may cause cerebral blood flow insufficiency which may worsen patient's condition.]
5) Elderly patients. [See “Use in the Elderly” section.]

2. Important Precautions
1) **In patient with bilateral or unilateral renal artery stenosis, renal function may be aggravated** rapidly due to decreased renal blood flow and decreased glomerular filtration pressure. **TANATRIL should not be used in these patients except the treatment with this product is judged to be essential.**
2) In **patients with hyperkalemia, the symptom may be aggravated. TANATRIL should not be used in these patients except the treatment with this product is judged to be essential.** In patients whose serum potassium levels tend to increase due to renal impairment and/or poorly controlled diabetes mellitus, etc. hyperkalaemia may occur. Serum potassium levels should be monitored carefully.
3) TANATRIL should be carefully administered while monitoring the patients’ conditions, since renal impairment, hyperkalaemia, and hypotension may occur when coadministered with aliskiren fumarate. TANATRIL should not be coadministered with aliskiren fumarate in patients with renal impairment whose estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73 m^2, except the case where treatment with this product is judged to be essential.
4) The following patients may present with **transient rapid decrease in blood pressure** after initial administration of this product. The treatment should be started at a lower dosage, and if the dosage increase is required, it should be done slowly while closely observing the patient's condition:
a. Patients with severe hypertension

b. Patients undergoing hemodialysis
c. Patients under treatment with diuretic antihypertensive drugs (especially those who have recently started taking these drugs)
d. Patients on a strict low-sodium diet

5) Since this product may induce dizziness or light-headedness due to its hypotensive action, patients should be cautioned against engaging in potentially hazardous activities, such as working at altitudes, operating machinery, or driving a vehicle.
6) It is recommended not to administer this product within 24 hours before surgery.
7) Dual blockade of 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 (see interactions). 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.

3. Drug Interactions

1) Contraindications for coadministration (TANATRIL should not be coadministered with the following drugs, etc.)

Drugs, etc.	Signs, Symptoms and Treatment.	Mechanism and Risk Factors
Apheresis by an adsorber using dextran sulfate-immobilized cellulose, tryptophanimmobilized polyvinyl alcohol or polyethylene terephthalate Liposorber® Immusorba TR® Cellsorba®, etc.	Shock may occur.	It is considered that bradykinin accumulated because negatively charged dextran sulfate-immobilized cellulose, tryptophan-immobilized polyvinyl alcohol or polyethylene terephthalate may promote the production of kinins in the blood, while this product may inhibit bradykinin metabolism.
Dialysis using acrylonitrile sodium methallyl sulfonate (AN69®)	Anaphylaxis may occur.	It is considered that bradykinin accumulated because AN69® membrane, a polyvalent ion substance, may promote the production of kinins in the blood, while this product may inhibit bradykinin metabolism.
Sacubitril valsartan sodium hydrate (Entresto)	Angioedema may occur. If the drug listed in the left column is administered, discontinue this product at least 36 hours prior to the administration. If this product is administered after the completion of	Concomitant use may additively inhibit bradykinin degradation and increase the risk of angioedema.

	administration of the drug listed in the left column, the interval between administrations should be at least 36 hours.	

2) Precautions for coadministration (TANATRIL should be administered with care when coadministered with the following drugs.)

Drugs, etc.	Signs, Symptoms and Treatment.	Mechanism and Risk Factors
Potassium- sparing diuretics (spironolactone, triamterene), Potassium supplements (such as potassium chloride)	Serum potassium levels may be increased. Serum potassium levels should be monitored carefully when coadministered with these drugs.	This product may decrease potassium excretion due to the decrease of aldosterone secretion as a result of the inhibition of angiotensin II production. Particular caution should be exercised in patients with renal impairment.
Aliskiren fumarate	Since renal impairment, hyperkalaemia and hypotension may occur, renal function, serum potassium levels and blood pressure should be monitored carefully. This product should not be coadministered with aliskiren fumarate in patients with renal impairment whose eGFR is less than 60 mL/min/1.73m^2, except the case where treatment with this product is judged to be essential.	Inhibitory action of this product on renin-angiotensin system may be increased when co-administered with the drug.
Angiotensin II receptor blockers	Since renal impairment, hyperkalaemia, and hypotension may occur, renal function, serum potassium levels, and blood pressure should be monitored carefully.	
Antihypertensive diuretic (such as trichlormethiazide, hydrochlorotiazide)	When this product is administered for the first time to patients on antihypertensive diuretics, hypotensive effects may be intensified. Therefore, these drugs should be administered with care by	Administration of this product may induce rapid decrease in blood pressure since plasma renin activity has been increased by diuretic treatment.

	starting the treatment at a lower dosage.	
Lithium preparations (lithium carbonate)	Lithium poisoning (such as sleepiness, tremor, confusion) may occur. Plasma concentrations of lithium should be measured periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	Reabsorption of lithium in renal tubule may be accelerated.
Nonsteroidal anti-inflammatory drugs (such as indomethacin)	The hypotensive action of this product may be reduced. Blood pressure should be observed periodically, and appropriate therapeutic measures should be taken.	It is considered that the hypotensive action of this product may be reduced due to the inhibitory effect of nonsteroidal anti-inflammatory drugs on prostaglandin synthesis.
	Renal function may be aggravated. If any abnormalities are observed, appropriate therapeutic measures such as discontinuation of administration should be taken	It is considered that renal blood flow is decreased due to the inhibitory effect of nonsteroidal anti-inflammatory drugs on prostaglandin synthesis.
Kallidinogenase preparations	Excessive decrease in blood pressure may occur when coadministered with these drugs.	Inhibitory action of this product on kinin degradation and kinin production induced by kallidinogenase may potentiate vascular smooth muscle relaxation.
Other drugs with antihypertensive effects (such as antihypertensive drugs, nitric acid preparations)	Hypotensive action may be intensified. Blood pressure should be measured periodically, and dosages of both drugs should be adjusted.	Effects (antihypertensive effects) may be intensified additively.

Clinical trial data has shown that dual blockade of renin-angiotensin- aldosterone-system (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 hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see Contraindications and Precautions).

4. Adverse Reactions

CLINICAL STUDIES (clinical trials)

Adverse reactions were reported in 50 (5.83%) of 858 patients treated. The major adverse reactions cough in 23 (2.68%), pharynx discomfort in 4 (0.47%), stomach discomfort in 2 (0.23%),

palpitation in 2 (0.23%). Among abnormal laboratory test values reported, 56 (6.53%), were suspected as related to TANATRIL, including increased ALT (GPT) in 15 (2.03%) of 739 patients, increased AST (GOT) in 13 (1.76%) of 739, increased creatinine in 6 (0.83%) of 722 patients.

Drug use-result survey (October 1993 to September 1999)
Adverse reactions were reported in 390 (6.75%) of 5,774 patients. The major adverse reactions were cough in 275 (4.76%), hypotension in 15 (0.26%), dizziness in 13 (0.23%), headache in 11 (0.19%), pharynx strange sensation and/or discomfort in 8 (0.14%), light-headedness in 8 (0.14%) and, rash in 7 (0.12%).

(1) Clinically significant adverse reactions
1) **Angioedema**, characterized by facial, tongue, glottic and/or laryngeal swelling associated with dyspnoea may occur (incidence unknown due to spontaneous reports). If any abnormalities are observed, the administration should be discontinued immediately, and appropriate therapeutic measures, such as administrations of antihistaminic drugs or adrenal corticosteroids and airway control, should be taken.
2) Serious **thrombocytopenia** (<0.1%) may occur. In this case, administration should be discontinued immediately and appropriate therapeutic measures should be taken.
3) **Acute renal failure** (incidence unknown due to spontaneous reports) or **aggravation of renal function disorder** (<0.1%) may occur. The patients should be observed carefully using renal function tests. If any abnormalities are observed, appropriate therapeutic measures, such as discontinuation of administration should be taken.
4) Serious hyperkalemia (<0.1%) may occur. The patients should be observed carefully. If any abnormalities are observed, appropriate therapeutic measures should be taken immediately.
5) **Erythroderma (Exfoliative dermatitis, oculomucocutaneous syndrome (Stevens Johnson syndrome), and pemphigus-like symptoms** (incidence of these symptoms unknown due to spontaneous reports) may occur. If any signs of erythema, blisters, pruritus, fever, enanthema are observed, administration should be discontinued and appropriate therapeutic measures should be taken.

(2) Clinically significant adverse reactions (similar drugs)
1) **Pancytopenia** has been reported in other angiotensin-converting enzyme inhibitors. If any signs or symptoms are observed, administration should be discontinued immediately and appropriate therapeutic measures should be taken.
2) **Pancreatitis** has been reported in other angiotensin-converting enzyme inhibitors. If increased blood levels of amylase, lipase are observed, appropriate therapeutic measures such as discontinuation of administration, should be taken.
(3) Other adverse reactions.
If any adverse reactions are observed, appropriate measures, such as discontinuing administration, should be taken.

Incidence / Type	0.1% to <5%	< 0.1%	Incidence unknown Note)
Hematologic	-	Decreased erythrocytes, decreased haemoglobin, decreased haematocrit, decreased platelet, decreased white blood cell, increased eosinophil	-
Renal	Increased serum creatinine, increased BUN	Proteinuria	-
Psychoneurotic	Headache, lightheadedness, dizziness	Dizziness on standing up, insomnia	Sleepiness
Cardiovascular	Hypotension	Palpitation	-
Respiratory	Cough, pharynx abnormal feeling and/or discomfort	Sputum, hoarseness	-
Gastrointestinal	-	Nausea, queasy, vomiting, stomach discomfort, abdominal pain, anorexia, diarrhea	-
Hepatic	Increased AST (GOT), increased ALT (GPT)	Increased ALP, increased LDH, jaundice	Increased γ-GTP
Hypersensitivity	Rash, pruritus	-	Photosensitivity, urticaria
Others	Increased serum potassium	Tinnitus, dysgeusia, thirst, increased CK (CPK), chest discomfort, fatigue, malaise, oedema, facial flushing	Alopecia, numbness, feeling of weakness, hypoglycaemia

Note) Incidence unknown due to spontaneous reports

5. Use in the Elderly

TANATRIL should be administered with care such as starting from a lower dosage (e.g., 2.5 mg) while carefully monitoring of the patient's conditions.

1) This product is mainly excreted by the kidney. Elevated blood concentrations of this product may persist, and adverse reactions are likely to occur or effects are likely to be intensified because elderly patients often have reduced renal function.

2) In general, excessive decrease in blood pressure is considered undesirable in the elderly patients. (Cerebrovascular disorders, such as cerebral infarction, may occur.)

6. Use in Patients with Reproductive Potential

6.1 Women of childbearing potential

Cases have been reported in which angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used in women without recognizing that the woman were pregnant, and foetal and neonatal adverse events (renal failure, aplasia of skull, lung, and kidney, death, etc.) were observed.

Prior to administration, the necessity of administration of this drug should be carefully considered, taking into account whether alternative drugs are available, etc., and this drug should be administered only if the potential therapeutic benefits are considered to outweigh the potential risks. If administration is considered necessary, attention should be paid to the following points.

1) Prior to administration of this drug, the absence of pregnancy should be confirmed. Also, during administration of this drug, the absence of pregnancy should be confirmed periodically. When pregnancy is detected, administration of this drug should be discontinued immediately.
2) The following matters should be explained to patients at the start of administration of this drug. In addition, an explanation should be provided during administration when necessary.
   - This drug can cause foetal and neonatal harm when used to a pregnant woman.
   - If pregnancy is detected or suspected, the attending physician should be consulted immediately.
   - If pregnancy is planned, the attending physician should be consulted.

6.2 Pregnant Women

This drug is contraindicated to pregnant women or women who may be pregnant. When pregnancy is detected during treatment, this product should be discontinued immediately. Oligohydramnios, fetal or neonatal deaths, neonatal hypotension, renal failure, hyperkalemia and contracture of the limbs, craniofacial deformation, or pulmonary hypoplasia supposedly due to cranial hypoplasia and oligohydramnios have been reported in patients receiving angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers during mid or late pregnancy. It was reported in overseas retrospective epidemiologic investigations that patients receiving angiotensin-converting enzyme inhibitors during the early pregnancy had increased relative risk of major congenital malformations of fetal as compared with the patients who had no antihypertensive drugs.

6.3 Breast-feeding Women

This product should not be administered to nursing mothers. If administration of this product is judged to be essential, breast-feeding should be discontinued during treatment. [Animal studies (in rats) have shown that this product is excreted in breast milk.]

7. Pediatric use

The safety of TANATRIL in children has not been established (no clinical experience).

8. Precautions concerning use

Precautions regarding dispensing tablets:

For drugs that are dispensed in a press-through package (PTP), instruct the patients to remove this product from the PTP sheet prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]

9. Other Precautions

It has been reported that hypoglycaemia is likely to occur when an angiotensin-converting enzyme inhibitor is coadministered during treatment with insulin or oral hypoglycemic drug.

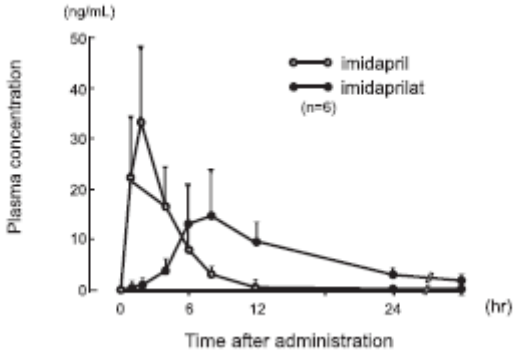
PHARMACOKINETICS

Imidapril hydrochloride is metabolized to 4 metabolites, which were detected and identified, in addition to unchanged imidapril hydrochloride. The di-carboxylic acid form (imidaprilat) alone is pharmacologically active among the 4 metabolites.

1. Absorption

Following single oral administration of 10 mg of imidapril hydrochloride in healthy subjects, imidapril hydrochloride reached the peak plasma concentration in about 2 hours and was eliminated from the plasma with a half- life of about 2 hours. Imidaprilat, the active metabolite of imidapril, reached the peak plasma concentration (about 15 ng/mL) 6 to 8 hours after administration, and was gradually eliminated from the plasma with a half- life of about 8 hours.

2. Metabolism and excretion
Following single oral administration of 10 mg of imidapril hydrochloride in healthy subjects, 25.5% of the dosage was excreted in the urine within 24 hours.



3. Accumulation
The plasma concentration of imidaprilat reached the steady state 3 to 5 days after the initiation of repeated oral administration of 10 mg of imidapril hydrochloride once a day for seven days in healthy subjects; there was no sign of accumulation. In patients with impaired renal function, peak plasma imidaprilat levels increased, and its elimination from the plasma may be delayed.

CLINICAL STUDIES
TANATRIL was evaluated by clinical trials, including double blind comparative clinical trials, at 133 institutions.
1) Essential hypertension (mild to moderate)
In clinical studies including a double blind comparative clinical trial, TANATRIL was effective in 80.8 % (361/447) of patients with mild to moderate essential hypertension.
2) Patients with severe hypertension and hypertensive patients with renal impairment
In clinical studies involving patients with severe hypertension and hypertensive patients with renal impairment TANATRIL was effective in 100 % (19/19) of the patients with severe hypertension and 84.0% (21/25) of the hypertensive patients with renal impairment.
3) Renal parenchymal hypertension
In a clinical study involving patients with renal parenchymal hypertension, TANATRIL was effective in 80.6% (25/31) of the patients.

PHARMACOLOGY
Imidapril hydrochloride is a prodrug which is hydrolyzed in the body after oral administration to form the di-carboxylic acid form (imidaprilat), an active angiotensin converting enzyme inhibitor. Imidaprilat inhibits the activity of ACE, an enzyme widely distributed in blood and endothelial cells of many tissues. The antihypertensive effects of imidapril hydrochloride are caused by ACE inhibition and the subsequent reduction in the formation of angiotensin II, which either directly or indirectly results in dilatation of peripheral vessels and reduction of vascular resistance.

1. Angiotensin converting enzyme inhibition
1) The active metabolite imidaprilat competitively inhibits the activity of ACE preparations derived from swine renal cortex and human serum in a dose-dependent manner.
2) In rats, orally administered imidapril hydrochloride and imidaprilat inhibit dose-dependently the elevation of blood pressure induced by angiotensin-I in a dose-dependent manner.

2. Antihypertensive action
1) Orally administered imidapril hydrochloride had significant dose-dependent antihypertensive effects in spontaneously hypertensive rats (SHR) and in 2-kidney-1-clip Goldblatt hypertensive rats. It had slight hypotensive effects in normotensive rats, but it was not effective in DOCA/saline hypertensive rats.
2) Oral administration of imidapril hydrochloride in SHR for 2 weeks had stable antihypertensive effects and had no effect on the heart rate.
3) Repeated oral administration of 5 to 10 mg of imidapril hydrochloride once a day in patients with essential hypertension had stable antihypertensive effects and had no effect on the circadian variation of blood pressure.

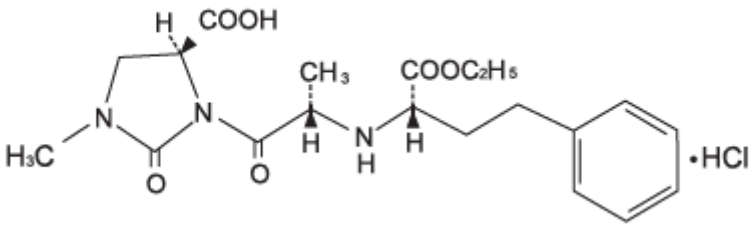
3. Other actions
1) Renal blood flow and glomerular filtration rate significantly increased in dogs after intravenous or intraduodenal administration of imidapril hydrochloride or imidaprilat.
2) In SHR, long-term treatment with imidapril hydrochloride for 9 to 10 weeks prevented the genetic hypertensive development and cardiac hypertrophy due to the hypertension.

PHYSICOCHEMISTRY
Non-proprietary name:
Imidapril hydrochloride

Chemical Name:
(4S)-3-{(2S)-2-[(1S)-1-Ethoxycarbonyl-3-phenylpropylamino]propanoyl}-1-methyl-2-oxoimidazolidine-4-carboxylic acid monohydrochloride

Molecular formula:
$C_{20}H_{27}N_3O_6$ HCl: 441.91

Structural formula:



Description:
- Imidapril hydrochloride occurs as white crystals. It is odorless or has a slightly characteristic odor.
- It is freely soluble in methanol, soluble in water, sparingly soluble in ethanol (99.5), and practically insoluble in ethyl acetate, in chloroform, in diethyl ether and in hexane.

PACKAGING

TANATRIL Tablets 5 mg

Boxes of 30 tablets (10 tablets X 3) in PTP

Boxes of 100 tablets (10 tablets X 10) in PTP

TANATRIL Tablets 10 mg

Boxes of 30 tablets (10 tablets X 3) in PTP

Boxes of 100 tablets (10 tablets X 10) in PTP

Under license from:
Mitsubishi Tanabe Pharma Corporation
Osaka, Japan

Manufactured by:
PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia

Product Registrant:
Mitsubishi Tanabe Pharma Singapore Pte. Ltd.

Marketed by:
Pharmaforte Singapore Pte Ltd