MAL

Mitsubishi Tanabe Pharma

SELECTIVE ANGIOTENSIN CONVERTING ENZYME INHIBITOR

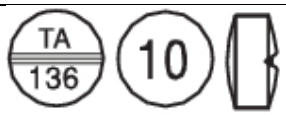
TANATRIL® Tablets 5 mg
TANATRIL® Tablets 10 mg
(Imidapril hydrochloride)

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

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 polyvinyl alcohol or polyethylene terephthalate [Shock may occur.] (See "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 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 PRECAUTIONS – Drug Interactions.)

DESCRIPTION

Brand name	TANATRIL Tablets 5 mg	TANATRIL Tablets 10 mg
Ingredient-content	Imidapril hydrochloride	
	5 mg per tablet	10 mg per tablet
Dosage form	Plain tablets	
Color	White	
Appearance		
Size	Diameter: 6.0 mm Thickness: 2.53 mm (2.45-2.60 mm)	Diameter: 6.5 mm Thickness: 2.55 mm (2.50-2.60 mm)
Weight	0.08 g	0.09 g
Identification code	TA 135	TA 136

INDICATIONS

Treatment of essential hypertension.

DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 5 mg to 10 mg of imidapril hydrochloride once a day. The dosage may be adjusted depending on the patient's age and symptoms.

< Precautions >

In patients with serious renal impairment whose creatinine clearance levels are less than 30 mL/ 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 PHARMACOKINETICS.)

PRECAUTIONS

ACE INHIBITORS

INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY.

1. Careful Administration (TANATRIL should be administered with care in the following patients.)

1) In patients with severe hypertension, hypertension with renal impairment, the recommended initial dose is 2.5 mg once a day. [See DOSAGE AND ADMINISTRATION – Precautions and PRECAUTIONS - Adverse reactions, Clinically significant adverse reactions.]
2) Patients with Hyperkalemia [See "Important Precautions" section.]
3) Patients with bilateral or unilateral renal artery stenosis. [See "Important Precautions" section.]
4) Patients with cerebrovascular disorders. [Excessive hypotension may cause cerebral blood flow insufficiency which may worsen patient's condition.]
5) Elderly patients. [See PRECAUTIONS - Use in the Elderly.]

2. Important Precautions

1) In patients with hyperkalemia, the symptom may be aggravated. This product 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. hyperkalemia may occur. Serum potassium levels should be monitored carefully.
2) Since the following patients may experience **transient excessive hypotension** after initiation of therapy with TANATRIL, the administration should be initiated with a reduced dosage; gradually increase the dosage while closely observing the patient's condition :
   (1) Patients with severe hypertension
   (2) Patients who undergo hemodialysis
   (3) Patients on diuretic therapy (especially those in whom diuretic therapy has been recently initiated)
   (4) Patients on strict dietary salt restriction
3) Since dizziness or light-headedness may occur due to hypotensive effect, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as driving a car, working at heights, or operating machinery, etc.

4) Administration is not recommended within 24 hours prior to surgery.
5) 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.
6) This product should be carefully administered while monitoring the patient's condition, since renal impairment, hyperkalemia, and hypotension may occur when the drug is coadministered with aliskiren fumarate. This product should not be coadministered with aliskiren fumarate in patient with renal impairment whose estimated glomerular filtration rate (eGFR) is less than 60mL/min/1.73 m^2, except the case where treatment with this product is judged to be essential.
7) In patients with diabetic nephropathy associated with type 1 diabetes mellitus, rapid aggravation of renal function or hyperkalemia may occur during the early stage of administration (within one month). Serum creatinine and serum potassium levels should be monitored during early stage of administration. If rapid aggravation of renal function or increased serum potassium levels is observed, appropriate therapeutic measures such as reducing the dosage or discontinuation of administration should be taken.
8) In patients with child-bearing 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. [See "Use during Pregnancy, Delivery or Lactation" section]
   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.
   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.

3. Drug Interactions

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

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Apheresis by an adsorber using dextran sulfate-immobilized cellulose, tryptophan-immobilized 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.
Aliskiren fumarate (Rasilez) (For use in patients with diabetes mellitus, except for patients with extremely poor blood pressure control despite other antihypertensive treatment)	Increased risks of nonfatal stroke, renal impairment, hyperkalaemia, and hypotension have been reported.	Concomitant use may enhance the inhibitory effect on the renin-angiotensin system.
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 administration of the drug listed in the left column, the interval between administrations should be at least 36 hours.	Concomitant use may additively inhibit bradykinin degradation and increase the risk of angioedema.

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

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Potassium-sparing diuretics (such as 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, hyperkalemia 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 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 diuretics (such as trichlormethiazide, hydrochlorothiazide)	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 starting the treatment at a lower dosage.	Administration of this product may induce rapid decrease in blood pressure since plasma renin activity has been increased by diuretic treatment.
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 indometacin)	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.

4. Adverse Reactions

CLINICAL STUDIES (clinical trial)

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

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%), rash in 7 (0.12%), etc.

(1) Clinically significant adverse reactions (rarely; <0,1%, no adverb : incidence is unknown due to spontaneous report).

1) **Angioedema**, manifested as swelling of the face, tongue, glottis and larynx accompanied by dyspnea, may occur. If any of these signs are observed, the drug should be discontinued immediately and appropriate measures, such as administrations of antihistaminic agents, adrenal cortex hormone agents, etc. and maintaining the airway, should be taken.
2) Severe **thrombocytopenia** may occur. In case, administration should be discontinued immediately and appropriate therapeutic measures should be taken.
3) Since **acute renal failure** and exacerbation of renal impairment may occur, the patient's clinical condition should be closely monitored by performing renal function test. If any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.
4) Severe hyperkalemia may occur. The patients should be observed carefully. If any abnormalities are observed, appropriate therapeutic measures should be taken immediately.
5) **Erythroderma (Exfoliative dermatitis), oculo-muco-cutaneous syndrome (Steven Johnson syndrome), and pemphigus- like symptoms** may occur. If symptoms such as erythema, blisters, pruritus, fever, enanthema, etc. are observed, the drug should be discontinued and appropriate measures should be taken.

(2) Clinically significant adverse reactions (similar drugs)

1) It has been reported that **pancytopenia** may occur with the use of other angiotensin converting enzyme inhibitors. If symptoms are observed, the drug should be discontinued immediately and appropriate measures taken.
2) It has been reported that **pancreatitis** may occur with the use of other angiotensin converting enzyme inhibitors. If increase in blood concentration of amylase, lipase, etc. is observed, appropriate measures such as discontinuing administration, should be taken.

(3) Other adverse reactions.

If any adverse reactions are observed, appropriate measures, such as discontinuing administration, should be taken.

	Incidence unknown	5% > ≥ 0.1%	<0.l%
Hematologic	…….	…….	A decrease in erythrocytes, hemoglobin, hematocrit, thrombocytes and leukocytes, an increase in eosinophil
Renal	…….	Increased serum creatinine and BUN	Proteinuria
Psychoneurologic	Sleepiness	Headache, light-headedness, dizziness	Dizziness on standing up, insomnia
Cardiovascular	…….	Hypotension	Heart pounding
Respiratory	…….	Cough, pharynx strange sensation and discomfort	Sputum, hoarseness
Gastrointestinal	…….	…….	Nausea, vomiting, stomach discomfort, abdominal pain, anorexia, diarrhea, queasy
Hepatic	Increased γ-GTP	Increased SGOT and SGPT	Increased Al-P and LDH, jaundice
Hypersensitivity	Photosensitivity, urticaria	Rash, pruritus	…….
Others	Alopecia, numbness, weakness, hypoglycemia	Increased serum potassium	Tinnitus, taste abnormality, thirsty, increased CPK, chest discomfort, fatigue, edema, facial hot flushes, dysgeusia, malaise

* lncidence unknown due to spontaneous reports

5. Use in the Elderly

Therapy should be instituted with special care, starting at a reduced dose (e.g., 2.5 mg) with careful monitoring of the patient's conditions.

1) TANATRIL is mainly excreted by the kidney. Since there is a possibility of persistent elevated blood concentrations in elderly patients, who often have impaired renal function, adverse reactions are more likely to occur and the action of the drug may be enhanced.
2) An excessive reduction in blood pressure is undesirable in elderly patients. (Cerebral infarction, etc., may occur.)

6. Use during Pregnancy, Delivery or Lactation

ACE INHIBITORS

INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY.

1) This drug is contraindicated to pregnant women or women who may be pregnant. When pregnancy is detected during treatment, this drug 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 (ACE) 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. [See “Important Precautions" section.]
2) Lactating mothers should not receive the drug. If use of the drug is judged to be essential, breast feeding should be discontinued during treatment. [It has been reported that imidapril hydrochloride is excreted in breast milk in animal experiments (rats).]

7. Pediatric use

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

8. Precautions concerning use

Precautions regarding dispensing :

Since TANATRIL is dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package 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. Symptoms and treatment overdosage

Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure. After ingestion of an overdosage, the patients should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Therapeutic measures depend on the nature and severity of the symptoms. Measurements to prevent absorption and hasten elimination such as gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after intake should be applied if ingestion is recent. If hypotension occurs, the patients should be placed in the stock position and salt and volume supplementation should be given rapidly. Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reaction should be treated by administering atropine. The use of pacemaker may be considered. Imidapril and imidaprilat may be removed from the circulation by haemodialysis. The use of highflux polyacrylonitrile membranes should be avoided.

10. Other Precautions

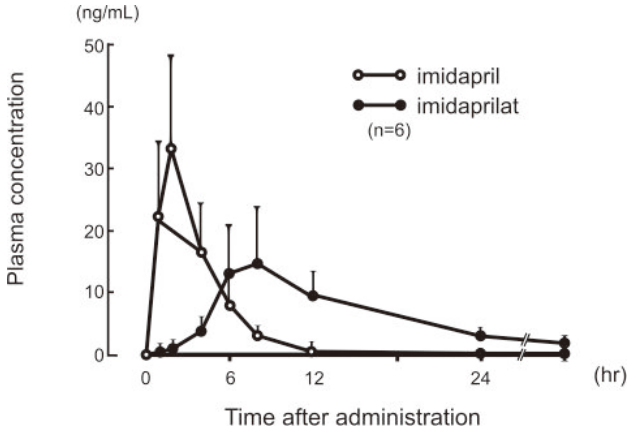
It has been reported that the concomitant use of angiotensin converting enzyme inhibitors with insulin or hypoglycemic agents may easily cause hypoglycemia.

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)
   ln 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 cell 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-l-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.

Storage

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

Expiration date

Indicated on the package and container. Shelf life: 48 months.

PACKAGING

Boxes of 30 tablets (10 tablets x 3) in Blister
Boxes of 100 tablets (10 tablets x 10) in Blister

Date of Revision : 1 July 2023

Under license from
Mitsubishi Tanabe Pharma Corporation
Osaka, Japan

Manufactured by
PT Mitsubishi Tanabe Pharma Indonesia
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