Revised: June 2022 (20th version, Section of Interactions, etc.)
Revised: November 2020 (19th version)

Antihypertensive Diuretic Agent
Prescription-only drug*1)
Japanese Pharmacopoeia
Furosemide Tablets

FUROSEMIDE TABLETS 40mg "TOWA"

Storage:
Protect from light and store at room temperature.
Expiration date:
Indicated on the package and label.

Standard Commodity Classification No. of Japan 872139	
Approval No.	21900AMX00722
Date of listing in the NHI reimbursement price	December 2007
Date of initial marketing in Japan	March 1974
Date of result of reevaluation	June 1994
Date of reevaluation (quality)	September 2003

*1) Caution – Use only pursuant to the prescription of a physician, etc.

CONTRAINDICATIONS (Furosemide Tablets is contraindicated in the following patients.)

1) Patients with anuria [Effects of this product are not expected.]
2) Patients with hepatic coma [Hypokalemia may occur and aggravate alkalosis, thereby aggravating hepatic coma.]
3) Patients in whom sodium and potassium in body fluid are clearly decreased [This product may cause electrolyte imbalance.]
4) Patients with a history of hypersensitivity to sulfonamide derivatives
5) Patients receiving desmopressin acetate hydrate (for nocturia due to nocturnal polyuria in males) (See "Interactions".)

COMPOSITION AND PRODUCT DESCRIPTION

Active ingredient per tablet	Furosemide (JP) ····· 40mg		
Inactive ingredient	Lactose Hydrate, Pregelatinized Starch, Corn Starch, Low Substituted Hydroxypropylcellulose, Magnesium Stearate		
Product description	White uncoated tablets with a score		
Identification code	Tablet	TwFRT	
	Package	Tw.FRT	
Appearance	Top surface	Bottom surface	Side surface
			
Diameter (mm)	8.0		
Thickness (mm)	3.0		
Weight (mg)	200		

INDICATIONS

Hypertension (essential, renal, etc), malignant hypertension, cardiac edema (congestive cardiac failure), renal edema, hepatic edema, premenstrual tension, edema caused by peripheral vascular disturbance, acceleration of elimination of urinary calculus

DOSAGE AND ADMINISTRATION

The recommended adult dosage is 40 to 80 mg of furosemide administered orally once daily or every other day. The dosage may be adjusted according to the patient's age and symptom. For patients with renal insufficiency or such, high-dose administration of this product may be allowed. However, for malignant hypertension, coadministration of this drug with other antihypertensive agents is recommended.

PRECAUTIONS

1. Careful Administration

(**Furosemide Tablets** should be administered with care in the following patients.)

1) Patients with advanced liver cirrhosis [Hepatic coma may be induced.]
2) Patients with serious coronary sclerosis or cerebral arteriosclerosis [When abrupt diuresis occurs, rapid plasma volume decrease and hemoconcentration may be developed and thromboembolism may be induced.]
3) Patients with serious renal dysfunction [Delayed drug excretion may lead to increased blood concentrations of this product.]
4) Patients with hepatic disease or hepatic dysfunction [Hepatic coma may occur.]
5) Patients with gout or diabetes mellitus or patients who have a parent, brother or sister with these diseases [Gouty may occur. Diabetes mellitus may be aggravated.]
6) Patients with diarrhea and vomiting [Electrolyte imbalance may occur.]
7) Preoperative patients [(1) The reactivity of the blood vessel wall to pressor amines may be reduced. (2) The paralytic effect of tubocurarine or such may be enhanced.] (See "Interactions".)
8) Patients receiving digitalis, glucocorticoids, ACTH or glycyrrhizin (See "Interactions".)
9) Patients during a low-sodium diet [Hyponatremia may occur.]
10) Elderly patients [See "Use in the Elderly".]
11) Pediatric patients (See "Pediatric Use".)
12) Patients with systemic lupus erythematosus [SLE may be aggravated.]

2. Important Precautions

1) Since diuretic effects of this product may abruptly occur, adequate attention should be paid to electrolyte imbalance and dehydration, treatment

should be started at a lower dosage, and the dosage should be gradually increased.

2) In case of continuous use, electrolyte imbalance may occur. Electrolyte tests should be conducted periodically.
3) Since dizziness and light-headed feeling resulting from hypotensive effect of this product may occur, patients should be cautioned when engaging in high-place work, operating potentially hazardous machinery or driving a car.
4) For patients who especially require nighttime rest, it is desirable to administer this product in the daytime in order to avoid nighttime urination.

3. Interactions

1) Contraindications for co-administration (Do not co-administer with the following.)

Drugs	Signs, Clinical Symptoms and Treatment	Mechanism and Risk Factors
Desmopressin acetate hydrate Minirinmelt (for nocturia due to nocturnal polyuria in males)	Hyponatremia may occur.	Both this product and desmopressin acetate hydrate may cause hyponatremia.

2) Precautions for co-administration (This drug should be administered with caution when co-administered with the following.)

Drugs	Signs, Clinical Symptoms and Treatment	Mechanism and Risk Factors
Pressor amines Adrenaline Noradrenaline	Coadministration of this product with pressor amines may reduce the effects of such amines. If pressor amines are to be administered preoperatively to a patient receiving this product, measures should be taken, including temporary suspension of this product.	Coadministration of this product with pressor amines is considered to reduce the reactivity of the blood vessel wall.
Tubocurarine and its analogues Tubocurarine chloride hydrate	Coadministration of this product with tubocurarine and its analogues may increase the paralytic effects of these drugs. If such drugs are to be administered preoperatively to a patient receiving this product, measures should be taken, including temporary suspension of this product.	The diuretic effect of this product decreases serum potassium, which is considered to intensify the neuromuscular blocking action of these drugs.
Other antihypertensive agents Beta-blockers etc.	Since coadministration of this product with other antihypertensive drugs may lead to increased antihypertensive effects, attention should be paid to dose adjustment and such of other antihypertensive drugs.	Coadministration of this product with other antihypertensive drugs with different mechanisms of action leads to increased antihypertensive effects.
Angiotensin-converting-enzyme (ACE) inhibitors Angiotensin II (A-II) receptor antagonists	If an ACE inhibitor or A-II receptor antagonist is administered to patients receiving this product who have previously been untreated with such drugs or if the doses of such drugs are increased in patients concurrently receiving this product, severely decreased blood pressure or aggravated renal function including renal failure may occur. When ACE inhibitors or A-II receptor antagonists are concomitantly used first time or the dose of these drugs is increased, consideration should be given to temporary suspension or dose reduction of this product.	Plasma renin activity is increased during treatment with this product. Coadministration with these drugs is considered to block the renin-angiotensin system, resulting in a sudden decrease in blood pressure.
Aminoglycoside antibiotics Gentamicin sulfate Amikacin sulfate	VIIIth cranial nerve disorders (hearing disorders) may increase in frequency and severity.	Coadministration of this product with these drugs may lead to increased concentrations of aminoglycoside antibiotics in the outer hair cells of the inner ear, resulting in necrosis of the outer hair cells and permanent deafness in some cases.
Cisplatin	Hearing disorders may increase in frequency and severity.	Coadministration of this product with cisplatin may lead to increased cisplatin concentrations in the outer hair cells of the inner ear, resulting in necrosis of the outer hair cells and permanent deafness in some cases.
Aminoglycoside antibiotics Gentamicin sulfate Amikacin sulfate Cephalosporin antibiotics Cefalotin sodium	Nephrotoxicity may increase in frequency and severity.	Sodium reabsorption in the proximal tubule is increased accompanied by increased reabsorption of antibiotics, which increases tissue concentrations of antibiotics, thereby increasing nephrotoxicity.
Digitalis preparations Digitoxin Digoxin	Since coadministration of this product with digitalis may increase the effect of digitalis on the heart, attention should be paid to serum potassium concentrations and blood digitalis concentrations.	The diuretic effect of this product decreases serum potassium, which leads to the binding of a large quantity of digitalis to myocardial Na^+/K^+-ATPase, causing increased cardiac contractility and arrhythmia.

Drugs	Signs, Clinical Symptoms and Treatment	Mechanism and Risk Factors
Glucocorticoids Hydrocortisone ACTH Glycyrrhizin preparations Stronger neo-minophagen C Formulations containing licorice	Excessively released potassium may cause hypokalemia.	Both drugs have a potassium excretion action.
Antidiabetic agents Sulfonylureas Insulin	The effects of anticiabetics may be significantly reduced.	Loss of intracellular and extracellular potassium causes inhibition of insulin secretion and decreased peripheral insulin sensitivity.
SGLT2 inhibitors	Coadministration of this product with these inhibitors may lead to increased diuretic effects. Blood pressure, pulse rate, urine volume, serum sodium concentrations and such should be monitored for the onset of dehydration. Caution should be exercised by dose adjustment or such of this product as necessary.	Increased diuretic effects may be observed.
Lithium Lithium carbonate	Since lithium toxicity may increase in frequency and severity, attention should be paid to blood lithium concentrations and such.	Renal lithium reabsorption is heightened, which leads to increased blood lithium concentrations.
Salicylic acid derivatives Sodium salicylate Aspirin	Salicylic acid derivative toxicity may occur.	This product and salicylic acid derivatives competitively acts at the site of renal excretion, which causes a delay in the excretion of salicylic acid derivatives, resulting in salicylism.
Nonsteroical anti-inflammatory analgesics Indomethacin	The diuretic effect of this product may be reduced.	Nonsteroidal anti-inflammatory analgesics inhibit renal prostaglandin synthesis , cause water and salt retention in the body, and antagonize action of diuretics.
Uricosuric agents Probenecid	The uricosuric effect of uricosuric drugs may be reduced.	The increase of uric acid reabsorption , which is the indirecr effect of this product, inhibits the action of uricosuric agents.
Carbamazepine	Symptomatic hyponatremia may occur.	Increased sodium excretion effects are observed, resulting in hyponatremia.
Other cardiotonics Colforsin daropart hydrochloride	The development of arrhythmia such as ventricular extrasystoles may be accelerated.	This product may cause electrolyte imbalance, and thus coadministration with cardiotonics may cause arrhythmia.
Ciclosporin	Gouty arthritis may occur.	Hyperuricemia caused by furosemide and inhibition of urate excretion by ciclosporin exacerbate adverse reactions.
V_2-receptor antagonists	Increased diuretic effects may be observed. Blood pressure, pulse rate, urine volume, serum sodium concentrations and such should be frequently monitored for the onset of dehydration.	The diuretic effect is increased.
Mozavaptan hydrochloride		
Aliskiren	Coadministration (on an empty stomach) decreases the Cmax and AUC of this product by 49% and 28%, respectively[1]. In case of coadministration, a decrease in diuretic effect should be monitored and the dosage of this product should be adjusted if necessary.	Mechanism unknown.

4. Adverse Reactions

No investigation such as a drug use investigation clearly showing the incidence of adverse reactions has been conducted.

1) Clinically significant adverse reactions (incidence unknown)

(1) **Shock, anaphylaxis**: Shock or anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this product should be discontinued and appropriate measures should be taken.

(2) **Aplastic anemia, pancytopenia, agranulocytosis, thrombocytopenia, pure red cell aplasia**: Aplastic anemia, pancytopenia, agranulocytosis, thrombocytopenia or pure red cell aplasia may occur. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

(3) **Bullous pemphigoid**: Bullous pemphigoid may occur. If such symptoms are observed, appropriate measures such as discontinuing administration should be taken.

(4) **Deafness:** Deafness may occur. If such symptoms are observed, appropriate measures should be taken, including discontinuation of this product.

(5) **Toxic Epidermal Necrolysis: TEN, Mucocutaneo-ocular syndrome (Stevens-Johnson syndrome) Erythema multiforme, acute generalized exanthematous pustulosis**: Toxic epidermal necrolysis, mucocutaneo-ocular syndrome (Stevens-Johnson syndrome) erythema multiforme or acute generalized exanthematous pustulosis may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

(6) **Ventricular arrhythmia (torsades de pointes):** Ventricular arrhythmia accompanied by hypokalemia may occur. If any such abnormalities are observed, appropriate measures should be taken, including discontinuation of this product.

(7) **Interstitial nephritis**: Interstitial nephritis may occur. If any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

(8) **Interstitial pneumonia:** Interstitial pneumonia may occur. If any such findings as cough, dyspnea, pyrexia, abnormal chest sound (lung crepitation) are

observed, examinations by such as chest X-ray and chest CT scan should be performed promptly. If interstitial pneumonia is suspected, this product should be discontinued, and appropriate treatment should be given, including corticosteroid therapy.

2) Other adverse reactions

	Incidence unknown
Hematologic*2)	Anemia, leukopenia, eosinophilia, hemolytic anemia
Abnormal metabolism*3)	Hyponatremia, hypokalemia, hypocalcemia, metabolic alkalosis, hyperuricemia, hyperglycemia, Hypertriglyceridemia, hypercholesterolemia, Pseudo-Barter syndrome
Dermatologic*2)	Rash, urticaria, redness, photosensitivity, pruritus, bullous dermatitis, purpura, lichenoid eruption
Gastrointestinal	Anorexia, diarrhea, nausea and vomiting, thirst, pancreatitis*4) (serum amylase increased)
Hepatic*2)	Jaundice, abnormality of hepatic function, cholestasis
Renal*5)	Increased BUN, increased creatinine
Psychoneurologic	Dizziness, headache, paresthesia, hearing impaired
Others	Weakness, malaise, orthostatic hypotension, muscle cramps, taste abnormality, angiitis、pyrexia

*2):If such symptoms are observed, administration of this product should be discontinued.

*3):If any abnormalities are observed, appropriate measures should be taken such as reduction of dosage or cessation of this product.

*4):Since pancreatitis has been reported, caution should be exercised to monitor for increased serum amylase levels.

*5):Appropriate measures should be taken such as discontinuation of this product.

5. Use in the Elderly

When this product is administered to elderly patients, the treatment should be started at a lower dosage and the patient's condition should be closely monitored with special attention to the following points.

1) In elderly patients, abrupt diuresis may cause decreased plasma volume, leading to dizziness on standing up, dizziness and syncope due to dehydration, hypotension, etc.
2) Especially in elderly patients with edema due to heart disease etc., abrupt diuresis may cause rapid decrease of plasma volume and hemoconcentration, and may induce thromboembolism such as cerebral infarction.
3) An excessive reduction in blood pressure is undesirable in the elderly patients. (Cerebral infarction may occur.)
4) Hyponatremia and hypokalemia are likely to occur in elderly patients.

6. Use during Pregnancy, Delivery or Lactation

1) This product should be used in first pregnancy trimester or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product in first pregnancy trimester has not been established.]
2) Breast feeding should be discontinued during treatment. [This product transits into breast milk.]

7. Pediatric Use

1) Low birth weight babies: Low birth weight babies within a few weeks after birth who are suffering from respiratory distress may be placed at increased risk of patent ductus arteriosus after administration of this product. Nephrocalcinosis has been reported to have occurred in very low birth weight babies with edema due to patent ductus arteriosus and hyalinosis after administration of this product. This drug should be administered with caution.
2) **Infants:** Electrolyte imbalance is likely to occur in infants; therefore, this product should be administered with caution.

8. OVERDOSAGE

Signs and symptoms: Decreased blood pressure, abnormal electrocardiogram, thrombosis, acute kidney injury, delirium or such may occur due to electrolyte depletion and fluid loss.

Treatment: Gastric lavage and activated charcoal administration restrict absorption of this product. Water and electrolytes should be given while monitoring the patient's condition.

This product cannot be eliminated by hemodialysis.

9. Precautions Concerning Use

Precautions Concerning the Dispensing of the Drug:

For drugs that are dispensed in a PTP (press-through package) sheet, 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, causing perforation and resulting in severe complications such as mediastinitis.]

10. Other Precautions

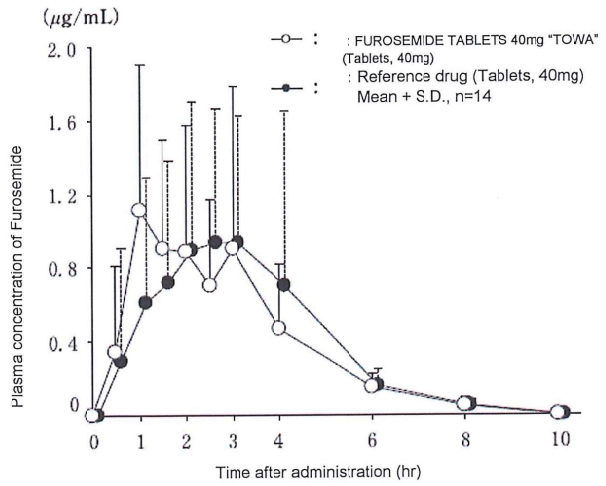
It has been reported that, in high risk patients of iodine contrast media induced radiocontrast nephropathy, the incidence of aggravated renal function after administration of the contrast media was higher in patients who receive furosemide compared to the patients receiving only hospital solution before the contrast media administration.

PHARMACOKINETICS

1. Bioequivalence test

<Reference data>

One tablet each of FUROSEMIDE TABLETS 40mg "TOWA" and a reference drug (as 40 mg of furosemide) were administered orally as a single dose to healthy adult men under fasting conditions (n=14) in a crossover design to measure each unchanged drug concentration in plasma. Obtained pharmacokinetic parameters (AUC and Cmax) were statistically analyzed. The analysis results confirmed the bioequivalence of these drugs. (based on PAB/PCD Notification No. 718, May 30, 1980)[2)]



	Determined parameter		Reference parameter	
	AUC_{10} (μg·hr/mL)	Cmax (μg/mL)	Tmax (hr)	MRT* (hr)
FUROSEMIDE TABLETS 40mg "TOWA" (Tablets, 40mg)	3.770±1.061	1.861±0.618	1.64±0.84	2.748±0.678
Reference drug (Tablets, 40mg)	3.912±1.504	1.990±0.868	1.96±1.01	3.011±0.651

(Mean ± S.D., n=14)
*MRT: Mean blood residence time

Plasma concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

2. Dissolution profile

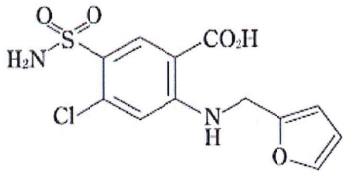
FUROSEMIDE TABLETS 40mg "TOWA" has been confirmed to conform to the dissolution standard of Furosemide Tablets defined in the official monographs of the Japanese Pharmacopoeia.[3]

PHARMACOLOGY

Furosemide is secreted from the proximal tubule via the organic anion transport system and inhibits Na^+-K^+-$2Cl^-$ symporter by acting on the lumen of the ascending limb of the loop of Henle to decrease NaCl reabsorption. This weakens the urine concentrating mechanism (countercurrent multiplication) and results in excretion of urine which is almost isotonic. Increased renal blood flow via increased biosynthesis of vasodilatory prostaglandins is also considered to be involved in the diuretic effect.[4]

PHYSICOCHEMICAL PROPERTIES

Structural formula:



Nonproprietary name:
Furosemide
Chemical name:
4-Chloro-2-[(furan-2-ylmethyl)amino]-5-sulfamoylbenzoic acid
Molecular formula:
$C_{12}H_{11}OIN_2O_5S$
Molecular weight:
330.74
Description:
Furosemide occurs as white, crystals or crystalline powder. It is freely soluble in *N*,*N*-dimethylformamide, soluble in methanol, sparingly soluble in ethanol (99.5), slightly soluble in acetonitrile and in acetic acid (100), and practically insoluble in water.
It dissolves in dilute sodium hydroxide TS.
It is gradually colored by light.
Melting point:
About 205°C (with decomposition).

PRECAUTIONS FOR HANDLING

Stability test

In an accelerated test using final packaged products (at 40°C and 75% relative humidity for 6 months), FUROSEMIDE TABLETS 40mg "TOWA" was estimated to be stable for 3 years under normal distribution conditions.[5]

PACKAGING

FUROSEMIDE TABLETS 40mg "TOWA":
Boxes of 100 tablets, 1,000 tablets (PTP)
Polyethylene containers of 1,000 tablets

REFERENCES

1) Vaidyanathan S.,et al. : Cardiovasc.Ther., 2008 ; 26(4) : 238-246
2) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test
3) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test
4) The 16th revision Japanese Pharmacopoeia explanatory, C-4257, 2011
5) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test

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