Revised: March 2023 (2nd version)
Revised: December 2022 (1st version)

Standard Commodity Classification No. of Japan
872133

Antialdosterone Diuretic and hypotensive Agent
Prescription-only drug Note)

Japanese Pharmacopoeia
Spironolactone Tablets

SPIRONOLACTONE TABLETS 25mg "TOWA"

Storage: Store at room temperature.
Shelf Life: 5 years
Note) Caution – Use only pursuant to the prescription of a physician, etc.

Approval No.	21800AMX10048
Date of Initial Marketing in Japan	Apr. 1978

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)

2.1 Patients with anuria or acute renal failure [Renal function may be further aggravated. In addition, decreased renal potassium excretion may induce or aggravate hyperkalemia.] [See 9.2.1 and 11.1.2]

2.2 Patients with hyperkalemia [Hyperkalemia may be aggravated.] [See 11.1.1]

2.3 Patients with Addison's disease [In Addison's disease, potassium excretion may be impaired due to decreased aldosterone secretion; therefore, hyperkalemia may occur in such patients.]

2.4 Patients under treatments with tacrolimus, eplerenone, esaxerenone or mitotane [See 10.1]

2.5 Patients with a history of hypersensitivity to this drug

3. COMPOSITION AND PRODUCT DESCRIPTION

3.1 Composition

Active ingredient per tablet	JP Spironolactone·····25 mg
Excipients	Lactose Hydrate, Corn Starch, Microcrystalline Cellulose, Low Substituted Hydroxypropylcellulose, Hydroxypropylcellulose, Magnesium Stearate, Titanium Oxide, l-Menthol

3.2 Product Description

Description/Dosage form		Slightly aromatic white tablets		
Identification code	Tablet	Tw SPL		
	Package	Tw. SPL		
Appearance		Top surface 	Bottom surface 	Side surface 
Diameter (mm)		9.0		
Thickness (mm)		3.3		
Weight (mg)		270		

4. INDICATIONS

- Hypertension (essential, renal, etc.)
- Cardiac edema (congestive cardiac failure), renal edema, hepatic edema, idiopathic edema, edema and ascites resulting from malignant tumor, malnutritional edema
- Alleviation of symptoms of diagnosed primary hyperaldosteronism

6. DOSAGE AND ADMINISTRATION

The recommended adult dosage is 50 to 100 mg of this drug administered orally in divided doses.
The dosage may be adjusted according to the patient's age and symptom.
However, this drug is often used in combination with other drugs for the indications other than "alleviation of symptoms of diagnosed primary hyperaldosteronism".

8. IMPORTANT PRECAUTIONS

8.1 Electrolyte abnormalities such as hyperkalemia may occur during continuous administration of this drug. Periodic examinations should be performed. [See 11.1.1]

8.2 Dizziness and such may occur due to the hypotensive action of this drug. Patients should be instructed to exercise caution when working in high places or operating machinery involving risks such as driving a vehicle.

8.3 It is recommended that patients who especially require to rest at night be administered with this drug in the morning so as not to wake up at night to urinate.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.1 Patients with Complication or History of Diseases, etc.

9.1.1 Patients with Serious Coronary Artery Arteriosclerosis or Cerebral Arteriosclerosis

If rapid diuresis develops, rapid decrease in plasma volume and hemoconcentration may occur, which may induce thromboembolism.

9.1.2 Patients under treatments with restricted sodium diet therapy

Fluid and electrolyte depletion may cause a predisposition to dehydration and hyponatremia. [See 11.1.1]

9.2 Patients with Renal Impairment

9.2.1 Patients with Acute Renal Failure

This drug should not be administered. Renal function may be further aggravated. In addition, decreased renal potassium excretion may induce or aggravate hyperkalemia. [See 2.1 and 11.1.2]

9.2.2 Patients with Serious Renal Disorders

Renal function may be further aggravated. In addition, decreased renal potassium excretion may induce or aggravate hyperkalemia.

9.3 Patients with Hepatic Impairment

Hyperkalemia may occur.

9.5 Pregnant Women

This drug should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

9.6 Brest-feeding Women

Continuation or discontinuation of breast-feeding should be considered in view of the therapeutic benefits of this drug and the benefits of breast-feeding. Canrenoic acid (the major active metabolite of Spironolactone) has been shown to be excreted in human breast milk.

9.7 Pediatric Use

There have been no clinical studies conducted in pediatric patients. Nursing infants are prone to electrolyte imbalance. [See 11.1.1]

9.8 Geriatric Use

When this drug 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.

9.8.1 Abrupt diuresis may cause decreased plasma volume, leading to dizziness on standing up, dizziness and syncope due to dehydration, hypotension, etc.

9.8.2 In elderly patients with heart disease or 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.

9.8.3 An excessive reduction in blood pressure is undesirable. Cerebral infarction may occur.

9.8.4 Since elderly patients often have decreased renal or hepatic function, hyperkalemia is likely to occur.

10. INTERACTINS

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

Drugs	Clinical Symptoms and Treatment	Mechanism and Risk Factors
Tacrolimus (Prograf) Eplerenone (Selara) Esaxerenone (Minnebro) [See 2.4]	Hyperkalemia may occur.	This drug and these drugs additively/ synergistically increase serum potassium levels.
Mitotane (Opeprim) [See 2.4]	The action of mitotane is inhibited.	This drug has been reported to inhibit the effect of mitotane.

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

Drugs	Clinical Symptoms and Treatment	Mechanism and Risk Factors
Antihypertensive Angiotensin-converting-enzyme (ACE) inhibitors Calcium antagonist agent β-Blocker Diuretic antihypertensive etc	Since coadministration of this drug and other antihypertensive drugs may lead to increased antihypertensive effects, caution should be exercised with dose adjustment and such.	Additive/synergistic effects of this drug and these drugs
* Potassium preparations Potassium chloride Potassium gluconate Potassium aspartate etc. Angiotensin-converting-enzyme (ACE) inhibitors Captopril Enalapril Lisinopril etc. Angiotensin II receptor antagonists Losartan potassium Candesartan cilexetil Valsartan etc. Aliskiren Potassium-sparing diuretics Triamterene Potassium canrenoate Cyclosporine Drospirenone	Hyperkalemia may be induced. Due caution should be exercised with close monitoring of serum potassium and such.	Increase in serum potassium level due to additive/synergistic effects of this drug and these drugs. Risk factors: Patients with renal disorders, elderly patients
* Finerenone	Since the risks of increased serum potassium and hyperkalemia may increase, co-administration with finerenone should be performed only if deemed therapeutically essential. If this drug is co-administered with finerenone, the patient's condition should be carefully monitored by more frequent serum potassium measurements, etc.	
Norepinephrine	Coadministration of this drug with norepinephrine has been reported to decrease the vascular reactivity of norepinephrine.	The mechanism by which this drug reduces the cardiovascular reactivity of norepinephrine has not fully been elucidated. Risk factor: Patients under anesthesia
Sodium lactate	Coadministration of this drug with sodium lactate may decrease the alkalinizing effect of sodium lactate.	This drug may induce hyperkalemic acidosis and may antagonize the alkalinizing effect of sodium lactate.
Ammonium chloride Cholestyramine	Coadministration of this drug with such drugs has been reported to cause metabolic acidosis.	Additive/synergistic effects of this drug and these drugs
Digoxin Metildigoxin	Coadministration of this drug with digoxin or metildigoxin may increase blood digoxin or metildigoxin concentrations.	This drug decreases renal excretion of digoxin and metildigoxin, which may lead to increased blood concentrations of digoxin and metildigoxin.
Digitoxin	Coadministration of this drug with digitoxin may increase or decrease the effect of digitoxin and should thus be cautiously performed under close monitoring including blood digitoxin concentration measurement.[1), 2)]	There have been reports indicating that the half-life of digitoxin in the blood is shortened due to the induction of hepatic enzymes by this drug. Although the mechanism is unknown, it has also been reported that the half-life of digitoxin in the blood was prolonged.
Lithium preparations Lithium carbonate	Coadministration of lithium with diuretics or ACE inhibitors has been reported to cause lithium poisoning. Attention should be paid to blood lithium concentrations.	It is considered that insufficient ionized sodium increases ionized lithium retention and thus coadministration of lithium with this drug causes lithium poisoning by facilitating sodium excretion.
Nonsteroidal anti-inflammatory drugs Indometacin etc.	Coadministration of these drugs with potassium-sparing diuretics has been reported to decrease the antihypertensive effects of such diuretics and to cause severe hyperkalemia in patients with renal impairment.	Inhibition of prostaglandin biosynthesis may lead to decreased antihypertensive effect due to sodium retention and to increased serum potassium due to potassium retention. Risk factor: Renal impairment

11. ADVERSE REACTIONS

Since the following adverse reactions may occur, patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

11.1 Clinically Significant Adverse Reactions

11.1.1 Electrolyte abnormalities (hyperkalemia, hyponatremia, metabolic acidosis, etc.) (incidence unknown)

Arrhythmia, general malaise, weakness and such may occur in association with electrolyte abnormalities. [See 2.2, 8.1, 9.1.2 and 9.7]

11.1.2 Acute renal failure (incidence unknown)

Acute renal failure may occur (accompanied by electrolyte abnormalities in some cases). [See 2.1 and 9.2.1]

11.1.3 Toxic Epidermal Necrolysis (TEN), Mucocutaneous- ocular syndrome (Stevens-Johnson syndrome) (both incidence unknown)

11.2 Other Adverse Reactions

	0.1% to less than 5%[a)]	Incidence unknown
Endocrine	Gynecomastia[b)], tumor of the breast, decreased libido, impotence, hairiness, irregular menstruation, amenorrhea, postmenopausal hemorrhage, low sound	Breast mass, mastalgia
Hypersensitivity	Rash, ulticaria,	Pruritus
Psychoneurologic		Vertigo, headache, numbness of limbs, nervousness, depressed state, anxiety feeling, mental confusion, ataxia, somnolentia
Hepatic		Increased AST, increased ALT, increased γ-GTP, increased Al-P, increased LDH, increased bilirubin
Renal		Increased BUN
Gastrointestinal	Anorexia, nausea and vomiting, thirst, diarrhea, constipation	
Hematologic		Leukopenia, thrombocytoperia
Others	Malaise, palpitations, pyrexia, chloasma	Muscle cramps, hair loss

a) Investigations to clarify the incidences of adverse reactions to this drug, such as drug use investigations, have not been conducted; therefore, the incidences listed above were tabulated with reference to data from literature, spontaneous reports and other relevant documents.
b) Gynecomastia is usually alleviated or resolved after dose reduction or treatment discontinuation, but may persist in rare cases.

13. OVERDOSAGE

13.1 Symptoms

Overdoses of this drug may cause nausea, vomiting, somnolence, mental confusion, maculopapular rash, erythema, diarrhea, electrolyte imbalance and dehydration.

13.2 Overdose management

Administration of this drug should be discontinued, and potassium intake including potassium from meals should be restricted

14. PRECAUTIONS CONCERNING USE

14.1 Precautions Concerning the Dispensing of the Drug

For drugs that are dispensed in a press-through package (PTP), patients should be instructed to remove the drug from the package prior to use. 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.

15. OTHER PRECAUTIONS

15.1 Information Based on Clinical Use

15.1.1 There have been case reports of breast cancer which occurred in patients (both male and female patients) treated with long-term oral administration of this drug.

15.1.2 There have been case reports of increased prostatic specific antigen (PSA) during coadministration with abiraterone acetate. This drug binds to androgen receptor and may increase PSA in patients with prostate cancer receiving abiraterone acetate.

15.2 Information Based on Nonclinical Studies

In a carcinogenicity study in rats in which this drug was administered orally for 24 months, tumors of endocrine organs and proliferative changes in the liver have been reported.

16. PHARMACOKINETICS

16.1 Blood Level

16.1.1 Bioequivalence test

One tablet each of SPIRONOLACTONE TABLETS 25mg "TOWA" and Aldactone-A Tablets 25mg (as 25 mg of spironolactone) were administered orally as a single dose to male rabbits (n = 10) in a crossover design to compare and investigate on unchanged drug concentrations in plasma. The results demonstrated no significant difference in bioavailability between these preparations.[3)]

16.4 Metabolism

The major metabolites detected in urine were canrenone, 6ß-hydroxy-7α-methyl-sulfinylspironolactone, and glucuronate conjugate of canrenoic acid (non-Japanese data).[4)]

16.5 Excretion

When a single dose of [20-^{3}H] spironolactone 200 mg was orally administered to healthy adult males, 31.6% and 22.7% of the radioactivity were excreted in urine and feces, respectively, over 5 days after administration (non-Japanese data).[4)]

18. PHARMACOLOGY

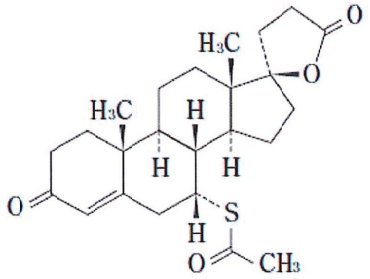
18.1 Mechanism of Action

Spironolactone is an antagonist of aldosterone, acting primarily at the aldosterone-dependent sodium-potassium exchange site in the distal renal tubule. Spironolactone promotes the excretion of sodium and water, but inhibits potassium excretion.[5), 6)]

- In a study using adrenalectomized rats administered with aldosterone, spironolactone exhibited dose-proportional anti-aldosterone action [based on urinary sodium/potassium (Na/K) ratio as an indicator].
- In a study using rabbits with experimental renal hypertension, decreased blood pressure, increased urinary excretion of sodium, increased urine output, and slightly decreased urinary excretion of potassium were observed.

19. PHYSICOCHEMICAL PROPERTIES

Structural formula:



Nonproprietary name: Spironolactone

Chemical name: 7α-Acetylsulfanyl-3-oxo-17α-pregn-4-ene-21,17-carbolactone

Molecular formula: $C_{24}H_{32}O_4S$

Molecular weight: 416.57

Description: Spironolactone occurs as a white to light yellow-brown fine powder. It is freely soluble in chloroform, soluble in ethanol (95), slightly soluble in methanol, and practically insoluble in water. It shows crystal polymorphism.

Melting point: 198 - 207°C (Insert the capillary tube into a bath at about 125°C, and continue the heating so that the temperature rises at a rate of about 10°C per minute in the range between 140°C and 185°C, and when the temperature is near the expected melting range, reduce the heating so that the temperature rises at a rate of about 3°C per minute.)

22. PACKAGING

100 tablets [10 tablets × 10: PTP]
1000 tablets [10 tablets × 100: PTP]
1000 tablets [bottle, with a desiccant]

23. REFERENCES

1) Carruthers, S. G. et al.: Clin Pharmacol Ther. 1980; 27(2): 184-187
2) Wirth, K. E. et al.: Eur J Clin Pharmacol. 1976; 9: 345-354
3) Internal data: Bioequivalence test
4) Karim, A. et al.: Clin Pharmacol Ther. 1976; 19(2): 158-169
5) Kagawa, C. M.: Endocrinology. 1960; 67: 125-132
6) Fukuchi, S. et al.: Tohoku J Exp Med. 1962; 76: 195-203

26. MARKETING AUTHORIZATION HOLDER, etc.

26.1 Marketing Authorization Holder

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