PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] TEVA-SPIRONOLACTONE/HCTZ

Spironolactone and Hydrochlorothiazide Tablets,

Tablets, 25 mg of spironolactone and 25 mg of hydrochlorothiazide
50 mg of spironolactone and 50 mg of hydrochlorothiazide, Oral

USP

Aldosterone Antagonist / Diuretic

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada M1B 2K9
www.tevacanada.com

Date of Initial Authorization:
June 28, 2011

Date of Revision:
October 20, 2022

Submission Control No: 264744

RECENT MAJOR LABEL CHANGES

WARNINGS AND PRECAUTIONS	**10/2022**

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Fixed-dose combination drugs are not indicated for initial therapy. Patients should be titrated on the individual drugs. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. If during maintenance therapy dosage adjustment is necessary, it is advisable to use the individual drugs.

TEVA-SPIRONOLACTONE/HCTZ (spironolactone and hydrochlorothiazide) is indicated for:

- **Edematous conditions for patients with**

  Congestive heart failure: For the management of edema and sodium retention when the patient is only partially responsive to, or is intolerant of, other therapeutic measures. The treatment of diuretic-induced hypokalemia in patients with congestive heart failure when other measures are considered inappropriate. The treatment of patients with congestive heart failure taking digitalis when other therapies are considered inadequate or inappropriate.

  Cirrhosis of the liver accompanied by edema and/or ascites: Aldosterone levels may be exceptionally high in this condition. TEVA-SPIRONOLACTONE/HCTZ is indicated for maintenance therapy together with bed rest and the restriction of fluid and sodium.

  The nephrotic syndrome: TEVA-SPIRONOLACTONE/HCTZ may be used in nephrotic patients who are not responsive to glucocorticoid therapy and who do not respond to other diuretics. However, spironolactone and hydrochlorothiazide has not been shown to affect the basic pathological process.

- **Essential hypertension**

  In patients with essential hypertension in whom other measures are considered inadequate or inappropriate. In hypertensive patients for the treatment of a diuretic induced hypokalemia when other measures are considered inappropriate.

1.1 Pediatrics

- Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of spironolactone and hydrochlorothiazide in pediatric patients has not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

- Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Caution is advised in patients with hepatic and/or renal impairment (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic and Renal sections).

2 CONTRAINDICATIONS

TEVA-SPIRONOLACTONE/HCTZ is contraindicated in:

- Patients who are hypersensitive to spironolactone, thiazides, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients who are allergic to sulfonamide-derived drugs.
- Patients with anuria.
- Patients with Addison's disease
- Patients with acute renal insufficiency or with severe impairment of renal function (GFR < 30 mL/Min/1.73 m^2)
- Patients with hyperkalemia
- Patients with hypercalcemia
- Women who are pregnant (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women)
- Nursing women (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.2 Breastfeeding)
- Combination with eplerenone (see 7 Warnings and Precautions- Hematologic - Hyperkalemia, 9 Drug Interactions sections)
- Combination with heparin, low molecular weight heparin (see 7 Warnings and Precautions- Hematologic - Hyperkalemia, 9 Drug Interactions sections)
- Patients with severe or progressive liver disease.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
Avoid potassium supplements, salt substitutes and foods containing high levels of potassium (e.g., bananas, prunes, raisins and orange juice)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Food effect on spironolactone and hydrochlorothiazide pharmacokinetics has been observed (see 9.5 Drug Food Interactions). Dose adjustment may be considered.

Optimal dosage should be established by individual titration of the components.

Treatment should be continued for 2 weeks before optimal effectiveness can be assessed.

4.2 Recommended Dose and Dosage Adjustment

Edema in adults: (congestive heart failure, hepatic cirrhosis or nephrotic syndrome): Daily dosage of 2 to 4 tablets of TEVA-SPIRONOLACTONE/HCTZ (25 mg/ 25 mg), or 1 to 2 tablets of TEVA-SPIRONOLACTONE/HCTZ (50 mg/ 50 mg) in single or divided doses should be adequate for most patients, but may range from 2 to 8 tablets daily of TEVA-SPIRONOLACTONE/HCTZ (25 mg/ 25 mg) or 1 to 4 tablets of TEVA-SPIRONOLACTONE/HCTZ (50 mg/ 50 mg) .

Edema in children: The usual daily maintenance dose of TEVA-SPIRONOLACTONE/HCTZ should be that which provides 1.65 to 3.3 mg of spironolactone per kilogram of body weight.

Essential hypertension: In essential hypertension, a daily dosage of 2 to 4 TEVA-SPIRONOLACTONE/HCTZ (25 mg / 25 mg) tablets or 1 to 2 TEVA-SPIRONOLACTONE/HCTZ (50 mg/ 50 mg) tablets in single or divided doses, will be adequate for most patients, but may range from 2 to 8 tablets of TEVA-SPIRONOLACTONE/HCTZ (25 mg/ 25 mg) or 1 to 4 tablets of TEVA-SPIRONOLACTONE/HCTZ (50 mg/ 50 mg).

Since TEVA-SPIRONOLACTONE/HCTZ increases the action of other antihypertensive drugs, especially the ganglionic blocking agents, the dosage of such drugs should be reduced by at least 50% when TEVA-SPIRONOLACTONE/HCTZ is added to the regimen.

4.4 Adminisrtation

TEVA-SPIRONOLACTONE/HCTZ is to be taken orally with or without food.

4.5 Missed Dose

In the event that a dose is missed, skip the missed dose and resume at the next scheduled dose. Do not double dose.

5 OVERDOSAGE

Symptoms: There have been no reports of fatal overdose in man (except indirectly through hyperkalemia). Nausea and vomiting occur, and (much more rarely) drowsiness, dizziness, decreased consciousness, coma, mental confusion, diarrhea, or a maculopapular or erythematous rash. These manifestations disappear promptly on discontinuation of medication. Hyperkalemia may be exacerbated. Thrombocytopenic purpura and granulocytopenia have occurred with thiazide therapy.

Treatment: No specific antidote. No persistent toxicity has occurred or is expected. Spironolactone/hydrochlorothiazide use should be discontinued and potassium intake (including dietary sources) restricted.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	**Tablet:** ▪ 25 mg of spironolactone and 25 mg of hydrochlorothiazide or ▪ 50 mg of spironolactone and 50 mg of hydrochlorothiazide	colloidal silicon dioxide, lactose monohydrate, magnesium stearate, natural peppermint flavour powder, Sodium lauryl sulfate and sodium starch glycolate, 25 mg of spironolactone and 25 mg of hydrochlorothiazide tablets also contain D&C Yellow #10 AL Lake HT, FD&C Yellow #6 AL Lake HT

Availability

TEVA-SPIRONOLACTONE/HCTZ 25 mg of spironolactone and 25 mg of hydrochlorothiazide:
Each ivory coloured, peppermint odour, round, bi-convex, compressed tablets; 25 over and under scoreline engraved on one side, **novo** engraved on the reverse contains 25mg of spironolactone and 25mg of hydrochlorothiazide.

Available in bottles of 100 tablets.

TEVA-SPIRONOLACTONE/HCTZ 50 mg of spironolactone and 50 mg of hydrochlorothiazide:
Each white coloured, peppermint odour, round, bi-convex, compressed tablets; 50 over and under scoreline engraved on one side, **novo** engraved on the reverse contains 50mg of spironolactone and 50mg of hydrochlorothiazide.

Available in bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Potassium (K^+) Supplementation: The concurrent administration of potassium supplements, a diet rich in potassium, or other K^+-sparing diuretics is not recommended as this may induce hyperkalemia.

Somnolence and dizziness: Somnolence and dizziness have been reported to occur in some patients sometimes leading to falls and fractures.

Carcinogenesis and Mutagenesis

Tumorigenicity: Spironolactone, in chronic toxicity studies, has been shown to be a tumorigen in rats. Breast cancer and other neoplasms (intestinal, pancreas, etc) have been reported in postmarket surveillance.

Non-melanoma skin cancer: An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin] after hydrochlorothiazide therapy was reported in some epidemiological studies. The risk may be higher with increasing cumulative use (see 8 ADVERSE REACTIONS, 8.5 Post Market Drug Adverse Reactions). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see 16 NON – CLINICAL TOXICOLOGY, Carcinogenicity – Hydrochlorothiazide).

Patients taking hydrochlorothiazide should be informed of the potential risk of NMSC. They should be advised to regularly check their skin for new lesions as well as changes to existing ones, and to promptly report any suspicious skin lesions. Patients should also be advised to limit exposure to sunlight, to avoid the use of indoor tanning equipment, and to use adequate protection (e.g. a broad spectrum sunscreen with a SPF of 30 or higher, clothing, and a hat) when exposed to sunlight or UV light to minimize the risk of skin cancer.

Alternatives to hydrochlorothiazide may be considered for patients who are at a particularly high risk for NMSC (e.g., light coloured skin, known personal or family history of skin cancer, ongoing immunosuppressive therapy, etc.) (see 8 ADVERSE REACTIONS, 8.5 Post Market Adverse Reactions).

Cardiovascular

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates or narcotics.

Driving and Operating Machinery

Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

Endocrine and Metabolism

Gynecomastia: Gynecomastia may develop with the use of spironolactone and healthcare professionals should be advised of its possible occurrence. The development of gynecomastia appears to be related to both dosage and duration of therapy and is normally reversible when the drug is discontinued. If gynecomastia develops, discontinue the drug. In rare instances some breast enlargement may persist.

Hyperchloremic metabolic acidosis: Reversible hyperchloremic metabolic acidosis, usually in association with hyperkalemia, has been reported to occur in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function. Caution should be used in treating patients with acute liver impairments, since vigorous diuretic therapy may precipitate hepatic encephalopathy.

Acidosis and renal function: Rare reports of acidosis have been reported with spironolactone and hydrochlorothiazide.

Hypochloremic alkalosis: Hypochloremic alkalosis occurs infrequently and is rarely severe. Unduly restricted dietary sodium may complicate therapy. A chloride deficit may be corrected by using ammonium chloride (except in renal or hepatic disease) and is largely prevented by a near-normal sodium/chloride intake.

Pathological changes in the parathyroid gland, with resultant hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

Thiazides may increase the concentration of blood uric acid. Caution is necessary in patients with hyperuricemia or a history of gout, because gout may be precipitated by thiazides. Dosage adjustment of anti-gout medications may be necessary.

In diabetic and prediabetic patients, thiazides may increase blood glucose concentrations. Dosage adjustments of insulin or hypoglycemic medications may be required.

Hematologic

Electrolyte Balance: Because of the diuretic action of TEVA-SPIRONOLACTONE/HCTZ, patients

should be carefully evaluated for possible disturbance of fluid and electrolyte balance, due to the possibility of hyperkalemia, hypochloremic alkalosis, hyponatremia and possible blood urea nitrogen (BUN) elevation, especially the elderly and/or patients with pre-existing impaired renal or hepatic function.

a) Hyperkalemia

Hyperkalemia may occur in patients treated with TEVA-SPIRONOLACTONE/HCTZ, if the potassium intake is excessive. This can cause cardiac irregularities, some of which may be fatal. Hyperkalemia may occur in the absence of excessive potassium intake, particularly in patients with impaired renal function, elderly patients, or patients with diabetes. Consequently, no potassium supplementation should ordinarily be given with TEVA-SPIRONOLACTONE/HCTZ. TEVA-SPIRONOLACTONE/HCTZ should not be administered concurrently with other potassium-sparing diuretics. Spironolactone and hydrochlorothiazide, when used with angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, angiotensin II antagonists, other aldosterone blockers, even in the presence of a diuretic, has been associated with severe hyperkalemia (see 9 DRUG INTERACTIONS**)**.

Concomitant use of spironolactone with heparin, low molecular weight heparin or other drugs or conditions known to cause hyperkalemia may lead to severe hyperkalemia (See 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS)

Hyperkalemia in Patients with Moderate to Severe Heart Failure

As hyperkalemia may be fatal, it is critical to monitor and manage serum potassium in patients with heart failure receiving TEVA-SPIRONOLACTONE/HCTZ. Avoid using other potassium-sparing diuretics. Avoid using oral potassium supplements in patients with serum potassium > 3.5 mEq/L. No information is available regarding patients with serum creatinine > 2.5 mg/dL or a recent increase in serum creatinine >25%. The recommended monitoring for potassium and creatinine is one week after initiation or increase in dose of spironolactone, monthly for the first 3 months, then quarterly for a year, and then every 6 months. Discontinue or interrupt treatment for serum potassium > 5 mEq/L or for serum creatinine > 4 mg/dL.

Hyperkalemia in Patients with Diabetes

Diabetic patients who are treated with TEVA-SPIRONOLACTONE/HCTZ should also be treated with caution as they have an increased risk of hyperkalemia. The status of the patient's renal function and serum potassium levels should be assessed prior to initiating treatment and repeated within a few days and a few weeks thereafter in the patient at risk, especially in elderly patients. The recommended monitoring for potassium and creatinine is one week after initiation or increase in dose of spironolactone, monthly for the first 3 months, then quarterly for a year, and then every 6 months.

Hyperkalemia can be treated promptly by rapid intravenous administration of glucose (20 to 50%) and regular insulin, using 0.25 to 0.5 units of insulin per gram of glucose. This is a temporary measure to be repeated if required. TEVA-SPIRONOLACTONE/HCTZ should be discontinued and potassium intake (including dietary potassium) restricted.

b) Hypokalemia

Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis or during concomitant use of loop diuretics, glucocorticoids, or adrenocorticotropic hormone (ACTH). Monitor serum potassium levels when using concomitantly with other drugs (such as aminoglycoside antibiotics, cisplatin, foscarnet, and amphotericin B) known to increase the risk of hypokalemia induced by thiazide diuretics.

Digitalis therapy may exaggerate the metabolic effects of hypokalemia especially with reference to myocardial activity. If hypokalemia occurs, TEVA-SPIRONOLACTONE/HCTZ should be discontinued and consideration given to one of the following therapeutic regimens:

1. use of hydrochlorothiazide alone with potassium supplementation as needed, or
2. use of spironolactone alone.

c) Hyponatremia

During the administration of TEVA-SPIRONOLACTONE/HCTZ, patients suffering from sodium depletion must be attentively monitored and signs of electrolyte imbalance must be carefully checked.

TEVA-SPIRONOLACTONE/HCTZ may, if administered concomitantly with other diuretics, cause or aggravate hyponatremia, as manifested by dryness of the mouth, thirst, lethargy, and drowsiness.

A true low-salt syndrome may develop with TEVA-SPIRONOLACTONE/HCTZ therapy and may be manifested by increasing mental confusion similar to that observed with hepatic coma. This syndrome was differentiated from dilutional hyponatremia in that it does not occur with obvious fluid retention. Its treatment requires that diuretic therapy be discontinued and sodium administered.

Hepatic/Biliary/Pancreatic

Impaired Hepatic Function: TEVA-SPIRONOLACTONE/HCTZ should be used with caution in patients with mild to moderate impairment of hepatic function, because minor alterations in electrolyte balance may precipitate hepatic coma. In the treatment of the edema/ascites of cirrhosis, when high doses of TEVA-SPIRONOLACTONE/HCTZ are required, it is recommended that the drug dosage be decreased before diuresis is complete, in order to avoid dehydration. If mental confusion occurs, TEVA-SPIRONOLACTONE/HCTZ should be temporarily discontinued.

Immune

Exacerbation or activation of systemic lupus erythematous has been reported for sulfonamide derivatives, including thiazides (see 8 ADVERSE REACTIONS section).

Monitoring and Laboratory Tests

General: TEVA-SPIRONOLACTONE/HCTZ therapy may result in a transient elevation of BUN, especially when azotemia exists at the beginning of treatment. This appears to represent a concentration phenomenon rather than renal toxicity, since the BUN returns to normal after TEVA-SPIRONOLACTONE/HCTZ is discontinued. Progressive elevation of BUN is suggestive of the presence of pre-existing renal impairment.

Several reports of possible interference with digoxin radioimmunoassays by spironolactone or its metabolites have appeared in the literature. Neither the extent nor the potential clinical significance of this interference (which may be assay-specific) has been fully established.

Discontinue spironolactone for at least 4, and preferably 7, days prior to plasma cortisol determinations, if they are to be done by the method of Mattingly, that is, by fluorometric assay. No interference has been demonstrated with the competitive protein binding technique or radioimmunoassay technique.

Thiazides may decrease serum PBI levels without evidence of alteration of thyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide therapy.

Adrenal Vein Catheterization and Plasma Renin Activity: Discontinue spironolactone several days prior to adrenal vein catheterization for measurement of aldosterone concentrations and measurements of plasma renin activity.

Neurologic

Lithium generally should not be given with diuretics. Thiazide diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Acute renal failure, sometimes fatal, has been observed. Lithium dose adjustment may be required (see 9 DRUG INTERACTIONS).

Ophthalmologic

Choroidal Effusion, Acute Myopia and Secondary Angle-Closure Glaucoma: Thiazide, diuretics can cause an idiosyncratic reaction, resulting in choroidal effusion, acute transient myopia and/or acute angle-closure glaucoma. Symptoms include acute onset of decreased

visual acuity, blurred vision or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Renal

Thiazides should be used with caution in patients with renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Reproductive Health: Female and Male Potential

- **Fertility:** Spironolactone reduced fertility in female mice and increased the length of the estrous cycle in female rats (see 16 NON-CLINICAL TOXICOLOGY).

Skin

Photosensitivity: Photosensitivity reactions have been reported with the use of thiazide diuretics. If photosensitivity reactions occur during treatment with hydrochlorothiazide-containing drugs, treatment should be stopped.

7.1 Special Populations

7.1.1 Pregnant Women

see 2 CONTRAINDICATIONS

Spironolactone

There are no studies in pregnant women.

Spironolactone and its metabolites do cross the placental barrier and appear in cord blood.

Rabbits receiving spironolactone showed reduced conception rate, increased resorption rate, and lower number of live births. Dose-dependent decreased plasma prolactin and decreased ventral prostate and seminal vesicle weights in males, and increased luteinizing hormone secretion and ovarian and uterine weights in females were reported in offspring of rats exposed to spironolactone, that persisted into adulthood. Feminization of the external genitalia of male fetuses was reported in another rat study.

Thiazides

Thiazides cross the placental barrier and appear in cord blood. There is limited experience with thiazides during pregnancy, especially during the first trimester. Based on the pharmacological mechanism of action of thiazides their use during the second and third trimesters may decrease placental perfusion, increase uterine inertia, and inhibit labor, and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Thiazides should not be used for gestational edema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion.

Thiazides should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

TEVA-SPIRONOLACTONE/HCTZ is contraindicated during pregnancy.

7.1.2 Breast-feeding

see 2 CONTRAINDICATIONS

Spironolactone

Canrenone, a major (and active) metabolite of spironolactone appears in human breast milk.

Thiazides

Thiazides are excreted in human milk. Thiazides when given at high doses can cause intense diuresis which can in turn inhibit milk production. The use of TEVA-SPIRONOLACTONE/HCTZ during breast feeding is contraindicated. A decision should be made whether to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother. Certain adverse reactions to thiazide therapy (e.g. hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism) can occur in the newborn since thiazides have been demonstrated to appear in breast milk.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of spironolactone and hydrochlorothiazide in pediatric patients has not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Caution is advised in patients with hepatic and/or renal impairment (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS – Hematologic, Hepatic/Biliary/Pancreatic and Renal sections).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The adverse reactions encountered most frequently are gynecomastia and gastrointestinal symptoms. Adverse reactions due to spironolactone and hydrochlorothiazide are usually reversible upon discontinuation of the spironolactone and hydrochlorothiazide. In rare instances, some gynecomastia may persist.

A. Spironolactone

The adverse reactions encountered most frequently with spironolactone are gynecomastia and gastrointestinal symptoms. The following adverse reactions have been reported in association with spironolactone:

General disorders and administration site conditions: Malaise

Gastrointestinal disorders: Diarrhea and cramping, gastric bleeding, gastritis, nausea, ulceration, vomiting.

Blood and lymphatic disorders: Leukopenia (including granulocytosis), thrombocytopenia, anemia.

Immune system disorders: Drug fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis, pruritus, rash.

Hepatobiliary disorders: mixed cholestatic/hepatocellular toxicity (some fatal).

Metabolism and nutrition disorders: Electrolyte imbalance (hypochloremic alkalosis, hyponatremia, hypokalemia, hyperkalemia), see 7 WARNINGS AND PRECAUTIONS – Hematologic - Electrolyte Balance.

Musculokeletal, connective tissue and bone disorders: Muscle spasms, rhabdomyolysis, myalgia, weakness

Psychiatric disorders: Confusional state, libido disorders.

Nervous system disorders: Ataxia, headache, drowsiness, dizziness, lethargy.

Renal and urinary disorders: Renal dysfunction (including acute renal failure).

Reproductive system and breast disorders: gynecomastia (see 7 WARNINGS AND PRECAUTIONS- Endocrine and Metabolism), erectile dysfunction, inability to achieve or maintain erection, abnormal semen (decreased motility and sperm count), irregular menses or amenorrhea, postmenopausal bleeding, benign breast neoplasm, breast pain, breast carcinoma (including in male patients).

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), alopecia, hypertrichosis.

B. Hydrochlorothiazide

Cardiovascular: Orthostatic hypotension (may be potentiated by alcohol, barbiturates or narcotics).

Central Nervous System disorders: dizziness, vertigo, paresthesia, headache, xanthopsia.

Eye Disorders: acute myopia and acute angle closure glaucoma (see 7 WARNINGS AND PRECAUTIONS-Ophthalmologic).

Gastrointestinal disorders: anorexia, gastric irritation, nausea, vomiting, cramps, diarrhea, constipation, jaundice (intrahepatic cholestatic), acute pancreatitis, sialoadenitis.

Blood and lymphatic disorders: Leukopenia, thrombocytopenic purpura, agranulocytosis, aplastic anemia, hemolytic anemia.

Immune system disorders: purpura (including thrombocytopenic), photosensitivity, rash, urticaria, necrotizing angiitis, pruritus and erythema multiforme, respiratory distress including pneumonitis and pulmonary edema, fever, anaphylactic reactions.

Miscellaneous: Muscle spasm, weakness, restlessness, nitrogen retention, hypokalemia, hyperglycemia, glycosuria, hypomagnesemia, hyponatremia, hyperuricemia, transient blurred vision, alopecia.

Adverse reactions due to spironolactone and hydrochlorothiazide are usually reversible upon discontinuation of the spironolactone and hydrochlorothiazide. In rare instances, some gynecomastia may persist.

8.5 Post-Market Adverse Reactions

Non-melanoma skin cancer: Some pharmacoepidemiological studies have suggested a higher risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin with increasing use of hydrochlorothiazide. A systematic review and meta-analysis undertaken by Health Canada suggested, with important uncertainty, that the use of hydrochlorothiazide for several years (>3 years) could lead to:

- 122 additional cases (95% CI, from 112 to 133 additional cases) of SCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 3 observational studies);
- 31 additional cases (95% CI, from 24 to 37 additional cases) of BCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

Eye disorders: choroidal effusion, acute myopia, acute angle-closure glaucoma (frequency unknown).

Table 2 is based on post-marketing spontaneous adverse event reports. The percentages shown are calculated as the number of adverse events reported per 100 patient years exposure to spironolactone / hydrochlorothiazide. The causal relationship between spironolactone / hydrochlorothiazide and the emergence of these events has not been clearly established.

Table 2. Post-market Serious Spontaneous Adverse Event Reports

Adverse Event	***Estimated Reporting Rate***			
	Reported Commonly ≥ 1%	***Reported Uncommonly < 1% and ≥ 0.1%***	***Reported Rarely < 0.1% and ≥ 0.01%***	***Reported Very Rarely < 0.01%***
Blood and lymphatic system disorders				
Thrombocytopenia				X
Agranulocytosis				X
Anaemia				X
Leukopenia				X
Cardiac disorders				
Bradycardia (n=2)				X
Myocardialinfarction*				X
Tachycardia (n=1)				X
Arrythmia*				X
Atrioventricular block*				X
Atrial fibrillation*				X

Bundle branch block, Bundle branch block right*				X
Cardiac failure (+/-congestive) (n=1)				X
Right Ventricular failure*				X
Torsade de pointes*				X
Ear and labyrinth disorders				
Vertigo				X
Endocrine disorders				
Inappropriate ADH secretion (n=2)				X
ADH abnormality*				X
Hyperthyroidism*				X
Gastrointestinal disorders				
Vomiting				X
Nausea				X
Diarrhoea				X
Pancreatitis acute (necrotizing, relapsing)				X
Abdominal pain				X
Gastrointestinal haemorrhage (rectal haemorrhage)				X
Constipation				X
Melaena				X
General disorders and administration site conditions				
Malaise				X
Asthenia				X
Pyrexia				X
Chest pain				X
Oedema (peripheral + other)				X
Sudden death (n=1)*				X
Hepatobiliary disorders				
Jaundice				X
Cholestasis				X
Hepatitis*				X
Hepatomegaly*				X
Hepatic steatosis / necrosis / failure (reported 1 time each)				X
Infections and infestations				
Pneumonia*				X
Otitis media				X
Investigations				
Weight decreased*				X
Blood creatinine increased*				X
Gamma-glutamyltransferase				X

increased*				
Aspartate aminotransferase increased*				X
Alanine aminotransferase increased*				X
Transaminases increased*				X
Increased weight due to increased peripheral edema* (after switching to generic)				X
Immune system disorders				
Hypersensitivity				X
Metabolism and nutrition disorders				
Hyponatraemia				X
Hypomagnesaemia				X
Hyperkalaemia				X
Hypochloraemia				X
Hypercalcaemia				X
Dehydration				X
Decreased appetite				X
Metabolic acidosis				X
Increased abdominal fat tissue (after 1 year of treatment)*				X
Hypoglycaemia*				X
Musculoskeletal and connective tissue disorders				
Rhabdomyolysis*				X
Myalgia, Muscular weakness				X
Systemic lupus erythematosus				X
Neoplasms benign, malignant and unspecified (including cysts & polyps)				
Breast cancer (female, male)				X
Neoplasm malignant (n=2):				X
- Uterine leiomyoma*				X
- Adenocarcinoma pancreas (n=1)				X
- Hepatic cancer metastatic (n=1)				X
- Lung neoplasm malignant*				X
- Lymphoma				X
Nervous system disorders				
Somnolence				X
Dizziness / Balance disorder				X
Coma (Including Hepatic) (n=1)				X
Loss (n=1)/ Altered*/ Depressed* consciousness				X
Syncope*				X
Convulsions (n=1)				X

Cerebrovascular accident / disorder*				X
Brain oedema*				X
Paraesthesia				X
Psychiatric disorders				
Confusional state				X
Disorientation				X
Depression(n=1)				X
Aggression*				X
Agitation*				X
Abnormal behaviour*				X
Suicide attempt (n=1)*				X
Renal and urinary disorders				
Renal failure (acute, chronic)				X
Renal impairment				X
Tubulointerstitial nephritis*				X
Oliguria (n=1)				X
Anuria*				X
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				X
Pulmonary fibrosis (n=1)				X
Respiratory failure*				X
Pulmonary embolism (n=1)				X
Pulmonary oedema*				X
Interstitial lung disease*				X
Cough*				X
Skin and subcutaneous tissue disorders				
Purpura				X
Pruritus				X
Rash maculo-papular, erythematous				X
Photosensitivity reaction				X
Dermatitis bullous*				X
Eczema*				X
Toxic epidermal necrolysis / eruption*				X
Pemphigoid*				X
Vascular disorders				
Orthostatic hypotension				X
Hypotension				X
Circulatory collapse*				X
Arteriosclerosis (n=1)				X
Shock haemorrhagic (n = 1)*				X
Haemorrhage (n = 1)				X

Source: IMS exposure data from 2nd quarter 1998 to 1st quarter 2010; spironolactone /

thiazides cumulative report (Reporting Period: 10 November 1960 to 09 November 2009).

* The events indicated (*) have not been reported for spironolactone and hydrochlorothiazide, however, they have been reported for other spironolactone/thiazide combination products (spironolactone/butizide and spironolactone/ hydroflumethiazide).

n= number

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

TEVA-SPIRONOLACTONE/HCTZ is contraindicated in:

- Combination with eplerenone (see 7 WARNINGS AND PRECAUTIONS – Hematologic - Hyperkalemia, 9 DRUG INTERACTIONS sections).
- Combination with heparin, low molecular weight heparin (see 7 WARNINGS AND PRECAUTIONS – Hematologic - Hyperkalemia, 9 DRUG INTERACTIONS sections).

Potassium supplements are to be avoided.

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

The drugs listed in this section are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3. Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Alcohol, barbiturates or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics	Monitor serum potassium level.
Antidiabetic agents (e.g. insulin and oral hypoglycemic agents)	CT	Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance. Insulin requirements and dosage of hypoglycemic medication in diabetics may be increased, decreased or unchanged. Erythema multiforme was observed when spironolactone and hydrochlorothiazide and glibenclamide were coadministered.	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required. Hyperglycemia and glycosuria may be manifested in latent diabetics.
Antineoplastic drugs, including cyclophosphamide and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Antipyrine	---	Spironolactone enhances the metabolism of antipyrine.	
Atorvastatin* + furosemide + ASA	---	Hepatitis, pancreatitis, death have been reported with cotreatment with spironolactone and hydrochlorothiazide.	
Bile acid sequestrants (e.g.	CT	Bile acid sequestrants bind thiazide diuretics in the gut and impair	Give thiazide 2-4 hours before or 6 hours after

Proper/Common name	Source of Evidence	Effect	Clinical comment
Cholestyramine, Colestipol and Ammonium Chloride)		gastrointestinal absorption by 43-85%. Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothiazide by 30-35%. Hyperchloremic metabolic acidosis, frequently associated with hyperkalemic, has been reported in patients given spironolactone concurrently with ammonium chloride or cholestyramine.	the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary.
Calcium and vitamin D supplements	C	Thiazides decrease renal excretion of calcium and increase calcium release from bone.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal of calcium and/or vitamin D supplements may be necessary.
Carbamazepine	C	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur	Monitor serum potassium, and adjust medications, as required.
Digoxin	CT	Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity. Thiazide-induced electrolyte disturbances, i.e. hypokalemia and hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	It may be necessary to reduce the maintenance dose of digoxin when spironolactone is administered, and the patient should be carefully monitored to avoid over- or under-digitalization. Two mechanisms of

Proper/Common name	Source of Evidence	Effect	Clinical comment
			possible interaction: a) Spironolactone and its metabolites interfere with digoxin radioimmunoassay or b) alter the pharmacokinetics of digoxin. The occurrence of either or both of these processes may make interpretation of serum digoxin levels difficult. Concomitant administration of hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or thiazides, as required.
Diuretics and Antihypertensive Drugs	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACEI, ARB, and direct renin inhibitors). Hyperkalemia has been associated with the use of angiotensin converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, angiotensin II antagonists and aldosterone blockers in combination with spironolactone.	It is advisable to reduce the dose of these drugs. In particular, the dose of ganglionic blocking agents should be reduced by at least 50% when TEVA-SPIRONOLACTONE/HCTZ is included in the regimen.
Drugs known to cause hyperkalemia +	---	Concomitant use of drugs known to cause hyperkalemia with spironolactone may result in severe hyperkalemia.	

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs that alter GI motility, i.e., anti-cholinergic agents, such as atropine and prokinetic agents, such as metoclopramide, domperidone	CT, T	Bioavailability of thiazide diuretics may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	Dose adjustment of thiazide may be required.
Eplerenone	---	Severe hyperkalemia has been associated with the use of aldosterone blockers in combination with spironolactone.	
Gout medications (allopurinol, uricosurics, and xanthine oxidase inhibitors)	T, RC	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Dose adjustment of gout medications may be required.
Heparin, low molecular weight heparin	---	Concomitant use of spironolactone with heparin, low molecular weight heparin may lead to severe hyperkalemia.	
Lithium*	CT	Thiazide diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Cotreatment with Hydrochlorothiazide and spironolactone was associated with acute renal failure, sometimes fatal.	Concomitant use of thiazide diuretics with lithium is generally not recommended. If such use is deemed necessary, reduce lithium dose by 50% and monitor lithium levels closely.
Norepinephrine	---	Hydrochlorothiazide and spironolactone each reduce vascular responsiveness to norepinephrine.	Caution should be exercised in the management of patients subjected to regional or general anaesthesia while being treated with TEVA-

Proper/Common name	Source of Evidence	Effect	Clinical comment
			SPIRONOLACTONE/HCTZ. Consideration should be given to discontinuation of TEVA-SPIRONOLACTONE/HCTZ therapy prior to elective surgery.
Non-Steroidal Anti-Inflammatory Drugs (NSAID)	CT	It has been reported that nonsteroidal anti-inflammatory drugs such as ASA, mefenamic acid, and indomethacin may attenuate the natriuretic efficacy of diuretics due to inhibition of intrarenal synthesis of prostaglandins and have been shown to attenuate the diuretic action of spironolactone. Hyperkalemia has been associated with the use of indomethacin in combination with potassium-sparing diuretics. NSAID-related retention of sodium and water antagonizes the diuretic and antihypertensive effects of thiazides. NSAID-induced inhibition of renal prostaglandins leading to decreases of renal blood flow, along with thiazide-induced decreases in GFR may lead to acute renal failure. Patients with heart failure may be at particular risk.	However, it has been shown that ASA does not alter the effect of spironolactone on blood pressure, serum electrolytes, urea nitrogen, or plasma renin activity in hypertensive patients. If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustment may be required.
Selective serotonin reuptake inhibitors (SSRIs, e.g. citalopram, escitalopram, sertraline)	T, C	Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Skeletal muscle relaxants of the	C	Thiazide drugs may increase the responsiveness of some skeletal	

Proper/Common name	Source of Evidence	Effect	Clinical comment
curare family, e.g., tubocurare		muscle relaxants, such as curare derivatives.	
Topiramate	CT	Additive hypokalemia. Possible thiazide-induced increase in topiramate serum concentrations.	Monitor serum potassium and topiramate levels. Use potassium supplements, or adjust topiramate dose as necessary.

* Occurrence of death

Legend: C = Case Study; RCS = Retrospective Cohort Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Salt substitutes and foods containing high levels of potassium are to be avoided.

Food increased both rate (C_{max}) and extent (AUC) of exposure to spironolactone and its active metabolite, canrenone, following a 200 mg dose of spironolactone (given as two 100 mg tablets). In a 9 subject study, statistically significant increases of approximately 2-fold in spironolactone $AUC_{(0-24)}$ and greater than 2-fold in C_{max} were reported after food co-administration. At the same time, increases of approximately 1.4-fold were seen in C_{max} and $AUC_{(0-24)}$ of canrenone. The clinical importance of increased exposure due to co-administration with food has not been studied. However, if TEVA-SPIRONOLACTONE/HCTZ is administered with food, patients should be monitored for signs that can be associated with excessive exposure such as increased serum potassium levels and other serious symptoms (see 5 OVERDOSAGE section), particularly in patients with impaired renal and hepatic function, pregnant/nursing women and elderly patients.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Thiazides should be discontinued before carrying out tests for parathyroid function. Thiazides may also decrease serum protein-bound iodine (PBI) levels without evidence of alteration of thyroid function. It was shown that hydrochlorothiazide is effective in increasing 24h ^{131}I uptake rate and augmenting ^{131}I absorbed dose of thyroid remnant.

Several reports of possible interference with digoxin radioimmunoassay assays by

spironolactone, or its metabolites, have appeared in the literature. Increase of spironolactone concentrations by 2-4 fold 2-24h post-dose after coadministration with digoxin in healthy volunteers. Also, increase of digoxin levels when given with spironolactone. Hence, dose adjustment for both TEVA-SPIRONOLACTONE/HCTZ and digoxin is necessary and safety monitoring required.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

TEVA-SPIRONOLACTONE/HCTZ (spironolactone and hydrochlorothiazide) is a combination of two diuretic agents with different but complementary mechanisms and sites of action, thereby providing additive diuretic and antihypertensive effects. Additionally, the spironolactone component helps to minimize the potassium loss, which may be induced by the thiazide component. The diuretic effect of spironolactone is mediated through its action as a specific pharmacologic antagonist of aldosterone, primarily by competitive binding to receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. HCTZ promotes the excretion of sodium and water primarily by inhibiting their reabsorption in the cortical diluting segment of the distal renal tubule.

Both spironolactone and hydrochlorothiazide reduce exchangeable sodium and plasma volume, body weight, and blood pressure. The diuretic and antihypertensive effects of the individual components are potentiated when spironolactone and HCTZ are given concurrently.

10.2 Pharmacodynamics

Spironolactone is effective in lowering the systolic and diastolic blood pressure in patients with primary hyperaldosteronism. It is also effective in most cases of essential hypertension, despite the fact that aldosterone secretion may be within normal limits in benign essential hypertension.

10.3 Pharmacokinetics

No pharmacokinetic studies have been performed on spironolactone/HCTZ. Pharmacokinetic studies have been performed on the individual components of spironolactone/HCTZ.

The effects of hydrochlorothiazide will be observed on the day of administration, but the spironolactone component does not attain its maximal effect until the third day.

Following oral administration of 500 mg titrated spironolactone in five healthy male volunteers (fasting state), the total radioactivity in plasma reached a peak between 25 – 40 minutes. Although the absolute bioavailability of spironolactone was not determined, the extent of absorption was estimated to be 75%, as 53% of the dose was excreted in the urine

during 6 days and approximately 20% in the bile. Spironolactone is rapidly and extensively metabolized to a number of metabolites including canrenone and the sulfur-containing 7-thiomethylspirolactone, both of which are pharmacologically active. Approximately 25 to 30% of the dose administered is converted to canrenone, which attains peak serum levels 2-4 hours after single oral administration of spironolactone. In the dose range of 25 mg to 200 mg, an approximately linear relationship exists between a single dose of spironolactone and plasma levels of canrenone.

Plasma concentrations of canrenone decline in two distinct phases, the first phase lasting from 3 to 12 hours, being more rapid than the second phase lasting from 12 to 96 hours. Canrenone clearance data, following multiple doses of spironolactone, indicate that accumulation of canrenone in the body with 100 mg once a day would be lower than with 25 mg four times a day. Both spironolactone and canrenone are more than 90-percent bound to plasma proteins.

Administration with food resulted in higher exposure of spironolactone and its metabolites compared to fasted conditions. Following a single oral dose of 200 mg spironolactone to nine healthy volunteers, the mean (± SD) $AUC_{(0-24)}$ of spironolactone increased from 288 ± 138 (empty stomach) to 493 ± 105 ng · mL^{-1} · hr (with food) (increase by 1.95 fold, $p < 0.001$). The corresponding increases of the $AUC_{(0-24)}$ of metabolites were 7α-thiomethylspirolactone by 1.45-fold, 6β-hydroxy-7α- thiomethylspirolactone by 1.22-fold, and canrenone by 1.41-fold.

In one pharmacokinetic study in five healthy male volunteers receiving 500 mg of spironolactone, 47% to 57% of the dose was excreted in the urine within 6 days and the remaining amount could be detected in the feces (total recovery 90%). In another study of five healthy men, a single dose of spironolactone 200 mg (with radioactive tracer) was administered and in 5 days, 31.6% ± 5.87% of the radioactivity was excreted in the urine mainly as metabolites and 22.7% ± 14.1% in the feces.

Table 4. Pharmacokinetic Parameters of Spironolactone and its Metabolites in Healthy Volunteers following the Administration of Spironolactone 100 mg daily for 15 days

	Mean C_{max} (ng/mL)	Mean T_{max} (h)	Mean Post-Steady State t½ (h)	Accumulation Factor: $AUC_{0-24\ h,\ Day\ 15}$ / $AUC_{0-24\ h,}$ Day 1
7-α-(thiomethyl) spirolactone (TMS)	391	3.2	13.8	1.25
6-β-hydroxy-7-α-(thiomethyl) spirolactone (HTMS)	125	5.1	15.0	1.50
Canrenone (C)	181	4.3	16.5	1.41
Spironolactone	80	2.6	~1.4 ($t_{½}$ ∃)	1.30

Absorption

Hydrochlorothiazide is rapidly absorbed following oral administration, with onset of action occurring within one hour, and the duration of action is 6 to 12 hours. Plasma concentration attains a peak at 1 to 2 hours and declines with a half-life of 4 to 5 hours. Hydrochlorothiazide undergoes only slight metabolic alteration and is excreted in the urine.

Following single oral administration of HCTZ (25, 50, 100, and 200 mg) in 12 healthy volunteers, the extent of absorption ranged between 50% and 63% with peak plasma concentrations occurring at approximately 2 hours in all treatment groups. Absorption of oral HCTZ was independent of dose.

Concurrent administration of HCTZ with food has resulted in significant decreases in plasma drug levels as compared to the administration of HCTZ in a fasted state. Eight healthy volunteers were administered HCTZ as three single-dose oral treatments: one 50 mg tablet with 250 mL of water (fasting), with 20 mL of water (fasting) or 250 mL of water following a standard breakfast (fed). Mean peak HCTZ plasma levels of 310 ng/mL and 291 ng/mL were obtained in the two fasting treatment groups, as compared to a peak level of 241 ng/mL observed in the fed state.

Distribution:

It is distributed throughout the extracellular space, with essentially no tissue accumulation except in the kidney. HCTZ is approximately 40% protein bound and accumulates in erythrocytes by an unknown mechanism. The ratio between red blood corpuscles and plasma is 3.5:1. The volume of distribution of HCTZ is approximately 3 L/kg to - 4 L/kg.

Elimination

Following oral administration of four different doses (12.5 mg, 25 mg, 50 mg and 75 mg) of HCTZ to eight healthy volunteers, renal clearance ranged between 319 and 345 mL/min. HCTZ is excreted completely unchanged in the urine and appears in urine within 1 hour of dosing. Approximately 50% to 70% was recovered in the urine 24 hours after the oral administration of 25 mg to 65 mg of HCTZ.

Special Populations and Conditions

- **Pediatrics:** No pharmacokinetic studies have been performed with spironolactone/HCTZ in the pediatric population. Therefore, safety and effectiveness in pediatric patients have not been established.

- **Geriatrics:** No pharmacokinetic studies have been performed with spironolactone/HCTZ in the elderly population. Caution is advised in patients with hepatic and/or renal impairment (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic and Renal sections).

- **Hepatic Insufficiency:** No pharmacokinetic studies have been performed with spironolactone/HCTZ in patients with hepatic insufficiency. Caution is advised in patients with mild to moderate impairment. TEVA-SPIRONOLACTONE/HCTZ may also be contraindicated in acute progressive or severe hepatic failure (see 2 CONTRAINDICATIONS).

- **Renal Insufficiency:** No pharmacokinetic studies have been performed with spironolactone/HCTZ in patients with renal insufficiency. TEVA-SPIRONOLACTONE/HCTZ is contraindicated in patients with anuria, acute renal insufficiency, or significant impairment of renal function (see 2 CONTRAINDICATIONS).

11 STORAGE STABILITY AND DISPOSAL

Store between 15°C to 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

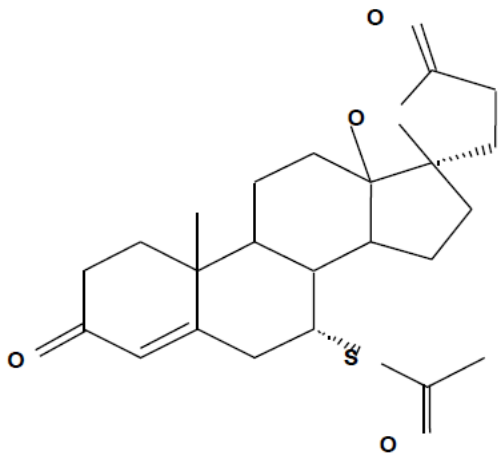
Drug Substance

A. Proper name: Spironolactone

Chemical name: 17β-hydroxy-7α-acetylthio-3-oxo-pregn-4-ene-21-carboxylic acid γ-lactone

Molecular formula and Molecular mass: $C_{24}H_{32}O_4S$ and 416.59 g/mol

Structural formula:



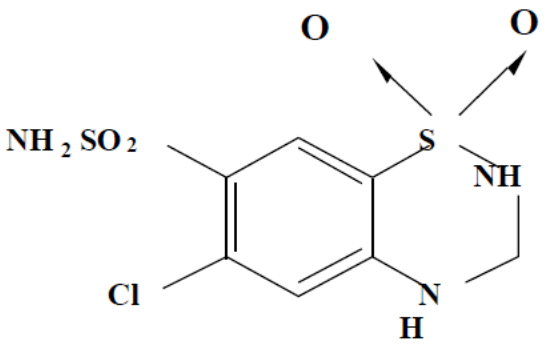
Physicochemical properties: Spironolactone is an off-white, micronized powder with a slightly bitter taste. It is practically insoluble in water, soluble in chloroform, ethanol, ethyl acetate and slightly soluble in methanol.

B. Proper name: Hydrochlorothiazide

Chemical name: 6-chloro-3.4-dihydro-2H-l.2.4-benzothiadiazine-7-sulphonamide l,1-dioxide

Molecular formula and Molecular mass: $C_7H_8ClN_3O_4S_2$ and 297.75 g/mol

Structural formula:



Physicochemical properties: A white, or practically white, practically odourless, crystalline powder; slightly soluble in water.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The clinical trial data on which the original indication was authorized is not available.

14.3 Comparative Bioavailability Study

A blinded, single dose, randomized, two-way, crossover comparative bioavailability study of TEVA-SPIRONOLACTONE/HCTZ 25 mg / 25 mg tablets (Teva Canada Limited) and ALDACTAZIDE® 25 mg / 25 mg tablets (G.D. Searle & Co. Ltd., Canada), administered as an 8 x 25 mg / 25 mg dose, was carried out in 12 healthy adult subjects under fasting conditions. A summary of the bioavailability data is presented in the following tables:

Spironolactone **(8 x 25 mg spironolactone / 25 mg hydrochlorothiazide)** Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	2642.7 2681.2 (17.7)	2723.5 2748.3 (14.2)	97.0	93.2-101.1
AUC_I (ng·h/mL)	3237.2 3294.1 (19.2)	3313.9 3348.7 (15.0)	97.7	92.7-103.0
C_{max} (ng/mL)	242.3 246.3 (20.0)	264.49 268.4 (18.1)	91.6	84.0-99.9
T_{max}[3] (h)	3.7 (24.3)	3.1 (22.6)		
$T_{½}$[3] (h)	8.6 (21.6)	8.3 (21.4)		

[1] TEVA-SPIRONOLACTONE/HCTZ (spironolactone and hydrochlorothiazide) 25 mg / 25 mg tablets (Teva Canada Limited).

[2] ALDACTAZIDE® (spironolactone and hydrochlorothiazide) 25 mg / 25 mg tablets (G.D. Searle & Co. Ltd., Canada).

[3] Expressed as the arithmetic mean (CV%) only.

Hydrochlorothiazide (8 x 25 mg spironolactone / 25 mg hydrochlorothiazide) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	6197.6 6325.0 (20.3)	6336.9 6452.0 (19.2)	97.8	94.3-101.4
AUC_I (ng·h/mL)	6801.1 6931.4 (19.3)	6872.5 6995.4 (19.1)	99.0	95.2-102.8
C_{max} (ng/mL)	800.1 807.7 (14.3)	753.4 765.5 (18.9)	106.2	101.2-111.4
T_{max}[3] (h)	2.5 (20.0)	3.0 (20.0)		
$T_{½}$[3] (h)	5.9 (11.9)	5.8 (10.9)		

[1] TEVA-SPIRONOLACTONE/HCTZ (spironolactone and hydrochlorothiazide) 25 mg / 25 mg tablets (Teva Canada Limited).

[2] ALDACTAZIDE® (spironolactone and hydrochlorothiazide) 25 mg / 25 mg tablets (G.D. Searle & Co. Ltd., Canada).

[3] Expressed as the arithmetic mean (CV%) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

A. Spironolactone

General Toxicology

Acute toxicity of spironolactone

Table 5 – Acute Toxicity of spironolactone

Species	Route	LD50 ± Standard Error (mg/kg)
Mouse	Intragastric	>1000
	Intraperitoneal	356 ± 94
Rat	Intragastric	>1000
	Intraperitoneal	786 ± 125
Rabbit	Intragastric	>1000

	Intraperitoneal	866 ± 156

Long-Term Toxicity

Table 6 – Long-term toxicity of spironolactone

Species / Number	Length of study	Dose (mg/kg/d)	Results
Spironolactone			
Rat (25/sex/gp)	26 w	0, 120, 300, 700	Only minor changes: dose-related increase in liver weights.
Rat (36/sex/gp)	78 w	0, 50, 150, 500	Significant dose-related increase in benign adenomas of thyroid follicular cells and testicular interstitial cells. In male rats, there was a dose-related increase in proliferative changes in the liver including hyperplastic nodules and hepatocellular carcinomas.
Rat (30/sex/gp)	104 w	0, 10, 30, 100	Dose-related increase in liver weights. The range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial stromal polyps in females.
Dog (2/sex/gp)	13 w	0, 12, 30, 70 (1-6 w); 100 (7-9 w); 250 (10-13 w)	No treatment-related findings.
Monkey (12/sex/gp)	26 w	0, 125	No treatment-related changes or tumors.
Monkey (4/sex/gp)	52 w	0, 20, 50, 125 (1-9 w); 0, 20, 50, 250	No tumors. Increased liver weights in males at high dose after 1 year. Dose-related increase of acinar tissue of mammary gland in males.
Potassium Canrenoate			

Rat (20M, 25F/gp)	26 w	0, 10, 60, 360	High dose: increased serum levels of albumin and protein in females. Increase in SGPT in males and females. Hypertrophy of thyroid and adrenal glands. Increase in hypertrophy of FSH cells. Mammary tumors (4 females), adenoma (1 rat), fibro-adenoma (1 rat), adenocarcinoma (1 rat, 60 mg/kg).
Rat (28/sex/gp) (8/sex/gp sacrificed at 13 w)	52 w	0, 30, 90, 270	Mammary tumors in 14 female rats (3 mid-doses, 8 high-dose). A dose-related (above 30 mg/kg/day) incidence of myeloid leukemia was observed in rats fed daily doses of potassium canrenoate.
Rat (60/sex/gp)	104 w	0, 20, 50, 125, 270	Myeloid leukemia and hepatic, thyroid, testicular and mammary tumors.
Dog (4/sex/gp)	26 w	0, 10, 45, 200	Hypertrophy of mammary glands with secretion of milky substance, increased uterine weight. Proliferation of pituitary cells producing prolactin, hyperplasia of the endometrium, atrophy of the prostate gland and hyperplasia of zona glomerulosa of the adrenal gland.

Seminal vesicles and prostate in rats, dogs and monkeys were significantly reduced in weight. There was a dose-related maturation arrest of the testes in rats treated for 78 and 104 weeks and monkeys treated for 52 weeks.

Genotoxicity

Neither spironolactone nor potassium canrenoate produced mutagenic effects in tests using bacteria. In the presence or absence of metabolic activation, spironolactone has not been shown to be genotoxic in mammalian tests *in vitro* and *in vivo.* Potassium canrenoate was genotoxic in some mammalian tests *in vitro*, in either absence or presence of metabolic activation, but was not genotoxic *in vivo*.

There was no increased incidence of leukemia in rats treated with spironolactone for up to 104 weeks at doses up to 500 mg/kg/day.

Reproductive and Developmental Toxicology

Teratology studies with spironolactone have been carried out in rodents and rabbits. Spironolactone at the dose of 20 mg/kg/day (2 times the maximum recommended human dose based on body surface area) caused a decreased conception rate, an increased rate of

resorption and a lower number of live fetuses in rabbits. Spironolactone has known endocrine effects in animals including progestational and antiandrogenic effects. Because of its antiandrogenic activity and the requirement of testosterone for male morphogenesis, spironolactone may have the potential for adversely affecting sex differentiation of the male during embryogenesis. When administered to rats at 200 mg/kg/day (10 times the maximum recommended human dose based on body surface area) between gestation days 13 and 21 (late embryogenesis and fetal development), feminization of the external genitalia of male fetuses was observed. Offspring of rats exposed during late pregnancy to 50 and 100 mg/kg/day doses of spironolactone exhibited changes in the reproductive tract including dose-dependent decreases in weights of the ventral prostate and seminal vesicle in males, increased ovary and uterus weights in females, and other indications of endocrine dysfunction (decreased basal plasma and pituitary prolactin in males and increased plasma luteinizing hormone), which persisted into adulthood.

Fertility

Spironolactone administered to female mice reduced fertility. Spironolactone (100 mg/kg/day, 2 times the maximum recommended human dose based on body surface area), injected intraperitoneally to female mice during a 2-week cohabitation period with untreated males, decreased the number of mated mice that conceived (effect shown to be caused by an inhibition of ovulation) and decreased the number of implanted embryos in those that became pregnant (effect shown to be caused by an inhibition of implantation), and at 200 mg/kg/day, also increased the latency period to mating.

In a three-litter reproduction study in which female rats received dietary doses of 15 and 50 mg spironolactone/kg/day, there were no effects on mating and fertility, but there was a 3-fold increase in incidence of stillborn pups at 50 mg/kg/day (24 times the maximum recommended human dose based on body surface area). When injected intraperitoneally into female rats (100 mg/kg/day for 7 days), spironolactone was found to increase the length of the estrous cycle by prolonging diestrus during treatment and inducing constant diestrus during a 2-week post-treatment observation period. These effects were associated with retarded ovarian follicle development and a reduction in circulating estrogen levels, which would be expected to impair mating, fertility and fecundity.

B. Hydrochlorothiazide

General Toxicology

Hydrochlorothiazide has been shown to be hepatotoxic (fatty degeneration, glycogen depletion, periportal inflammation) in rats. A significant reduction in serum potassium occurred. These hepatotoxic effects are not influenced by oral administration of potassium.

Dogs (N=40; 13-23 kg) administered oral hydrochlorothiazide (up to 200 mg/day) for up to 9

months, developed the following toxicity:

- significant hypercalcemia
- hypophosphatemia.
- Enlarged and hyperactive parathyroid glands.

Carcinogenicity

According to the experimental data available, hydrochlorothiazide revealed inconsistent evidence of carcinogenic activity in rats and mice, with conflicting evidence of hepatic adenoma in male mice at the highest dose and adrenal pheochromocytoma in one rat study but not in another. Current evidence is inadequate to draw a clear conclusion for a carcinogenic effect of hydrochlorothiazide in animals.

Genotoxicity

The mutagenic potential was assessed in a series of in vitro and in vivo test systems. While some positive results were obtained in vitro, all in vivo studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers in vitro and in the skin of mice following oral treatment. It is therefore concluded that although there is no relevant mutagenic potential in vivo, hydrochlorothiazide could enhance the genotoxic effects of UVA light. This mechanism of photosensitization could be associated with a higher risk for non-melanoma skin cancer.

Reproductive and Developmental Toxicology

Studies in which HCTZ was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 mg/kg and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus.

C. Spironolactone and Hydrochlorothiazide

General Toxicology

Long-Term Toxicity

Table 7 – Long-term toxicity of spironolactone and hydrochlorothiazide

	Length of study	**Dose (mg/kg/d)**	**Results**
Spironolactone And Hydrochlorothiazide			

Rat	4 mo	Ratio of spironolactone: hydrochlorothiazide (3:1) 56.3, 147.6, 149.7	Growth slightly but significantly retarded (high-dose male, low-dose female). Increased lipid in zona glomerulosa of the adrenals – not dose-related (in females more than males). Foci of myocardial necrosis (mainly low-dose males; one high-dose male; not significant in females)
Dog	4 mo	Ratio of spironolactone: hydrochlorothiazide (3:1) 60, 160	Slight increase, within the normal range in plasma non-protein nitrogen. Reduced potassium and chloride levels, especially in females.

Reproductive and Developmental Toxicology

Spironolactone and hydrochlorothiazide (0 and 20 mg/kg/day) was administered to albino rats from Day 5 to Day 15 of gestation. The only anatomic alterations in the test fetuses that differed significantly from controls were retarded closure of the skull and wavy appearing ribs in pups from two females. The incidence of retarded closure of the skull did not exceed that found in control groups in other studies. The significance of the wavy appearing ribs is unknown.

When spironolactone and hydrochlorothiazide (0 and 20 mg/kg/day) was administered to albino rabbits from Day 6 to Day 18 of gestation, no compound-related effects were noted.

17 SUPPORTING PRODUCT MONOGRAPH

1. ALDACTAZIDE (Tablets 25 mg / 25 mg and 50 mg / 50 mg), Submission Control No.: 253092, Product Monograph, Pfizer Canada ULC, January 25, 2022

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr TEVA-SPIRONOLACTONE/HCTZ

Spironolactone and Hydrochlorothiazide Tablets

Read this carefully before you start taking **TEVA-SPIRONOLACTONE/HCTZ** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment, and ask if there is any new information about **TEVA-SPIRONOLACTONE/HCTZ**.

Serious Warnings and Precautions

Avoid potassium supplements, salt substitutes and foods containing high levels of potassium (e.g., bananas, prunes, raisins, and orange juice). TEVA-SPIRONOLACTONE/HCTZ causes the kidney to eliminate unneeded water and sodium from the body into the urine, but also reduces the loss of potassium.

Follow your healthcare professional's directions for a low-salt or low-sodium diet and daily exercise program.

What is TEVA-SPIRONOLACTONE/HCTZ used for?

TEVA-SPIRONOLACTONE/HCTZ is used in adults to:

- lower high blood pressure
- treat fluid retention (edema) caused by heart, liver and kidney problems.

How does TEVA-SPIRONOLACTONE/HCTZ work?

TEVA-SPIRONOLACTONE/HCTZ contains a combination of 2 drugs, spironolactone and hydrochlorothiazide:

- Spironolactone belongs to a class of medicines known as aldosterone receptor antagonists. It is a diuretic or "water pill" that increases urination.
- Hydrochlorothiazide is also a diuretic or "water pill" that increases urination.
- Increasing urination lowers blood pressure.
- It also gets rid of extra fluid in fluid retention (edema).

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking TEVA-SPIRONOLACTONE/HCTZ regularly even if you feel fine. Do

not stop taking TEVA-SPIRONOLACTONE/HCTZ without talking to your healthcare professional.

What are the ingredient in TEVA-SPIRONOLACTONE/HCTZ?
Medicinal ingredients: Spironolactone and hydrochlorothiazide

Non-medicinal ingredients: Colloidal silicon dioxide, Lactose monohydrate, Magnesium stearate, Natural peppermint flavour powder, Sodium lauryl sulfate, Sodium starch glycolate.

25 mg of spironolactone and 25 mg of hydrochlorothiazide tablets also contain D&C Yellow #10 AL Lake HT, FD&C Yellow #6 AL Lake HT.

TEVA-SPIRONOLACTONE/HCTZ comes in following dosage forms:
Tablets:

- 25 mg of spironolactone and 25 mg of hydrochlorothiazide
- 50 mg of spironolactone and 50 mg of hydrochlorothiazide.

Do not use TEVA-SPIRONOLACTONE/HCTZ if:

- you are allergic to spironolactone or hydrochlorothiazide or to any non-medicinal ingredient in TEVA-SPIRONOLACTONE/HCTZ (see What are the ingredients in TEVA-SPIRONOLACTONE/HCTZ?) .
- you are allergic to sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in "-MIDE".
- you have difficulty urinating or produce no urine.
- you have severe kidney disease, severe liver disease or Addison's disease
- you have high levels of potassium (hyperkalemia) or calcium (hypercalcemia) in your blood.
- you are pregnant
- you are breastfeeding. TEVA-SPIRONOLACTONE/HCTZ passes into breast milk
- you are taking eplerenone, used to treat heart failure and high blood pressure.
- you are taking heparin or low molecular weight heparin, used to prevent blood clotting

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-SPIRONOLACTONE/HCTZ. Talk about any health conditions or problems you may have, including if you:

- are allergic to penicillin.
- have diabetes or are taking medicines for diabetes
- have liver or kidney problems.
- have or ever had lupus or gout.
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- are less than 18 years old.
- are taking a non-steroidal anti-inflammatory drug (NSAID) used to reduce pain and swelling. such as acetylsalicylic acid (ASA), ibuprofen, naproxen, and celecoxib.

- are taking an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in "PRIL". It lowers blood pressure.
- are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN". It lowers blood pressure
- are taking lithium used to treat bipolar disease
- are taking atorvastatin, used to lower cholesterol.
- are taking furosemide, a diuretic or "water pill" used to lower blood pressure.
- are having surgery (including dental surgery) and will be given an anesthetic. Be sure to tell the healthcare professional that you are taking TEVA-SPIRONOLACTONE/HCTZ.
- have had skin cancer or have a family history of skin cancer.
- have a greater chance of developing skin cancer because you have light-coloured skin, get sunburned easily, or are taking medicines to suppress your immune system.

Other warnings you should know about:

Risk of skin cancer:

- TEVA-SPIRONOLACTONE/HCTZ contains hydrochlorothiazide. Taking hydrochlorothiazide may increase your risk of developing non-melanoma skin cancer. The risk is higher if you have been taking TEVA-SPIRONOLACTONE/HCTZ for many years (more than 3) or at a high dose.
- While taking TEVA- SPIRONOLACTONE/HCTZ
  - Make sure to regularly check your skin for any new lesions. Check areas that are most exposed to the sun, such as the face, ears, hands, shoulders, upper chest and back.
  - You may become more sensitive to the sun while taking TEVA-SPIRONOLACTONE/HCTZ. Limit your exposure to the sun and to indoor tanning. Always use sunscreen (SPF-30 or higher) and wear protective clothing when going outside.
  - Talk to your healthcare professional immediately if you get more sensitive to the sun or UV light or if you develop an unexpected skin lesion (such as a lump, bump, sore, or patch) while you are taking TEVA- SPIRONOLACTONE/HCTZ.

Sudden eye problems:

- TEVA-SPIRONOLACTONE/HCTZ contains hydrochlorothiazide. Taking hydrochlorothiazide can cause serious eye problems. These eye problems are related and can happen within hours to weeks of starting TEVA-SPIRONOLACTONE/HCTZ.
- These eye problems include:
  - **Choroidal effusion:** An abnormal buildup of liquid in your eye that may result in vision changes.
  - **Myopia**: Sudden nearsightedness or blurred vision.
  - **Glaucoma**: An increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.
- If your vision changes, stop taking TEVA-SPIRONOLACTONE/HCTZ and get immediate medical help.

Breast development in males: TEVA-SPIRONOLACTONE/HCTZ contains spironolactone. Spironolactone can cause breast development in males. If you are male and develop tender or enlarged breast tissue while you are taking TEVA-SPIRONOLACTONE/HCTZ, talk to your healthcare professional.

Blood tests: TEVA-SPIRONOLACTONE/HCTZ can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Driving and using machines: TEVA-SPIRONOLACTONE/HCTZ can cause dizziness, lightheadedness, or fainting, especially after the first dose and when the dose is increased. This can sometimes lead to falls and broken bones. Alcohol, medicines used to reduce anxiety and help you sleep and strong pain killers called narcotics, can make these side effects worse. Do not drive a car or do other tasks that require attention until you know how TEVA-SPIRONOLACTONE/HCTZ affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not take TEVA-SPIRONOLACTONE/HCTZ together with:

- eplerenone, used to treat heart failure and high blood pressure.
- heparin or low molecular weight heparin used to prevent blood clotting.

You should also avoid taking potassium supplements while you are taking TEVA-SPIRONOLACTONE/HCTZ.

The following may interact with TEVA-SPIRONOLACTONE/HCTZ:

- Adrenocorticotropic hormone (ACTH) used to treat West Syndrome.
- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- Amphotericin B, used to treat fungal infections.
- Medicines used to treat cancer, including cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline.
- Medicines used to treat diabetes, including insulin and oral medicines.
- Bile acid resins used to lower cholesterol.
- Calcium or vitamin D supplements.
- Corticosteroids used to treat joint pain and swelling.
- Digoxin, a heart medication.
- Medications that slow down or speed up bowel function, including atropine,

metoclopramide, and domperidone.
- Medicines used to treat epilepsy, including carbamazepine and topiramate.
- Medicines that cause high levels of potassium in blood (hyperkalemia) including aminoglycoside antibiotics, cisplatin and foscarnet
- Gout medications, including allopurinol and probenecid.
- Lithium used to treat bipolar disorder (manic-depressive illness).
- Nonsteroidal anti-inflammatory drugs (NSAIDs), use to reduce pain and swelling, including ibuprofen, naproxen, and celecoxib.
- Other blood pressure lowering medications, including diuretics. When taken in combination with TEVA-SPIRONOLACTONE/HCTZ, they may cause excessively low blood pressure.
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocuranine.

How to take TEVA-SPIRONOLACTONE/HCTZ:

- Take TEVA-SPIRONOLACTONE/HCTZ exactly as prescribed by your healthcare professional.
- TEVA-SPIRONOLACTONE/HCTZ can be taken with or without food. If TEVA-SPIRONOLACTONE/HCTZ causes upset stomach, take it with food or milk. If you take TEVA-SPIRONOLACTONE/HCTZ with food and you have liver or kidney problems or are elderly, you must tell your healthcare professional. Taking TEVA-SPIRONOLACTONE/HCTZ with food can cause more medicine to be absorbed into your body which can increase your risk of certain side effects or overdose.
- TEVA-SPIRONOLACTONE/HCTZ is usually taken once a day in the morning. It is recommended that you take your dose at about the same time every day.

Usual Dose:

- **High blood pressure in adults:**
  TEVA-SPIRONOLACTONE/HCTZ (25 mg/25 mg): 2 to 4 tablets per day.
  TEVA-SPIRONOLACTONE/HCTZ (50 mg/50 mg): 1 to 2 tablets per day.
- **Fluid retention (edema) in adults**:
  TEVA-SPIRONOLACTONE/HCTZ (25 mg/25 mg): 2 to 4 tablets per day.
  TEVA-SPIRONOLACTONE/HCTZ (50 mg/50 mg): 1 to 2 tablets per day.
- **Fluid retention (edema) in children**: The healthcare professional will decide on the right dose based on their body weight.

Overdose

If you think you, or a person you are caring for, have taken too much TEVA-SPIRONOLACTONE/HCTZ contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Signs of overdose can include nausea, vomiting, drowsiness, dizziness, decreased alertness,

coma, mental confusion, diarrhea, red spots or rash on the skin, bruising, and high levels of potassium in your blood (stomach pain, chest pain, irregular heartbeat, muscle weakness, numbness). If you notice any of these symptoms while you are taking TEVA-SPIRONOLACTONE/HCTZ get immediate medical help.

Missed Dose:

If you have forgotten to take your dose during the day, carry on with the next dose at the usual time. Do not take a double dose to make up for a missed dose.

What are possible side effects from using TEVA-SPIRONOLACTONE/HCTZ?

These are not all the possible side effects you may have when taking TEVA-SPIRONOLACTONE/HCTZ. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- constipation
- diarrhea
- nausea, vomiting
- decreased appetite
- upset stomach, indigestion
- stomach pain and cramps
- enlargement of the glands in your mouth
- dryness of mouth
- dizziness, spinning sensation (vertigo)
- numbness and tingling
- headache
- drowsiness
- muscle cramps spasms, pain and/or weakness
- restlessness
- reduced libido
- In men: difficulty in getting or maintaining erections
- In women: breast discomfort, irregular or missed menstrual periods, postmenopausal bleeding
- rash

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional**	**Stop taking drug and get immediate medical help**

	Only if severe	In all cases	
COMMON			
Low Blood Pressure: Dizziness, fainting, lightheadedness. May occur when you go from sitting to standing up.	√		
Low Levels of Potassium in the Blood: Irregular heartbeats, muscle weakness, generally feeling unwell.		√	
Non-Melanoma Skin Cancer: lump or discoloured patch on the skin that stays after a few weeks and slowly changes. Cancerous lumps are red/pink and firm and sometimes turn into ulcers. Cancerous patches are usually flat and scaly.		√	
UNCOMMON			
Allergic Reaction: Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, redness, intense itching and burning.			√
Kidney Problems: Change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue.		√	
Liver Problems: Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.		√	
Increased Blood Sugar: Frequent urination, thirst.	√		
Electrolyte Imbalance: Weakness, drowsiness, muscle pain or cramps, rapid, slow or irregular heartbeat.		√	
Confusion		√	
Gynecomastia: Enlarged or painful breasts in men.		√	
Rapid, excessive weight loss		√	
Stomach Ulcer: burning pain in the gut, vomiting, vomiting blood.		√	
Lung Problems: Chest pain, difficulty			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
breathing.			**√**
RARE			
Low Levels of Platelets in the Blood: Bruising, bleeding, fatigue, weakness.		**√**	
Low levels of White Blood Cells: Infections, fatigue, fever, aches, pains, flu-like symptoms.		**√**	
VERY RARE			
Serious Skin Reactions (Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)): Severe skin peeling, scaling or blistering which may also affect your mouth, eyes, nose or genitals, itching, severe rash, skin pain, skin color changes (redness, yellowing, purplish), swelling and redness of eyes or face, flu-like feeling, fever, chills, body aches, swollen glands, cough			**√**
UNKNOWN			
Eye Problems: **-Choroidal effusion**: blind spots, eye pain, blurred vision **-Myopia:** Sudden near sightedness or blurred vision **-Glaucoma:** Increased pressure in your eye, eye pain			**√**
Anemia: Fatigue, loss of energy, weakness, shortness of breath.		**√**	
Inflammation of the Pancreas: Abdominal pain that lasts and gets worse when you lie down, nausea, vomiting.		**√**	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage

Store between 15°C to 30°C.

Keep out of the reach and sight of children.

If you want more information about TEVA-SPIRONOLACTONE/HCTZ:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9

Last revised: October 20, 2022