

## PRODUCT MONOGRAPH

### **PrTEVA-SPIRONOLACTONE/HCTZ**

Spironolactone and Hydrochlorothiazide Tablets, USP  
25 mg of spironolactone and 25 mg of hydrochlorothiazide  
50 mg of spironolactone and 50 mg of hydrochlorothiazide

#### **Aldosterone Antagonist with a Diuretic**

Teva Canada Limited  
30 Novopharm Court  
Toronto, Ontario  
Canada M1B 2K9  
[www.tevacanada.com](http://www.tevacanada.com)

**Date of Revision:**  
January 20, 2016

**Submission Control No: 190038**

## **Table of Contents**

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>3</b>
SUMMARY PRODUCT INFORMATION .....	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS .....	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS .....	9
DRUG INTERACTIONS .....	15
DOSAGE AND ADMINISTRATION .....	19
OVERDOSAGE .....	20
ACTION AND CLINICAL PHARMACOLOGY .....	20
STORAGE AND STABILITY .....	23
DOSAGE FORMS, COMPOSITION AND PACKAGING .....	23
 <b>PART II: SCIENTIFIC INFORMATION .....</b>	 <b>25</b>
PHARMACEUTICAL INFORMATION.....	25
TOXICOLOGY .....	28
REFERENCES .....	33
 <b>PART III: CONSUMER INFORMATION.....</b>	 <b>35</b>

**TEVA-SPIRONOLACTONE/HCTZ**

Spironolactone and Hydrochlorothiazide Tablets, USP

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Nonmedicinal Ingredients</b>
<b>oral</b>	<b>Tablet:</b> <ul style="list-style-type: none"><li>▪ 25 mg of spironolactone and 25 mg of hydrochlorothiazide or</li><li>▪ 50 mg of spironolactone and 50 mg of hydrochlorothiazide</li></ul>	Sodium lauryl sulfate, lactose monohydrate, colloidal silicon dioxide, sodium starch glycolate, natural peppermint flavour powder, magnesium stearate 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

**INDICATIONS AND CLINICAL USE**

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:

**1. 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.

## 2. 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.

### CONTRAINDICATIONS

**TEVA-SPIRONOLACTONE/HCTZ is contraindicated in:**

- Patients who are hypersensitive to spironolactone, thiazides, or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging Section.
- 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 ( $\text{GFR} < 30 \text{ mL/Min/1.73 m}^2$ )
- Patients with Hyperkalemia
- Patients with Hypercalcemia
- Women who are pregnant (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women)
- Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women)
- Combination with eplerenone ( see **Warnings and Precautions- Hyperkalemia, Drug Interactions sections**)
- Combination with heparin, low molecular weight heparin ( see **Warnings and Precautions- Hyperkalemia, Drug Interactions sections**)
- Patients with severe or progressive liver disease.

### WARNINGS AND PRECAUTIONS

**Avoid potassium supplements, salt substitutes and foods containing high levels of potassium** (e.g., bananas, prunes, raisins, and orange juice) Follow your doctor's directions for a low-salt or low-sodium diet and daily exercise program.

#### General

**Use only for "Indications":** Use TEVA-SPIRONOLACTONE/HCTZ (spironolactone and hydrochlorothiazide) only for conditions described under "INDICATIONS".

**Potassium ( $\text{K}^+$ ) Supplementation:** The concurrent administration of potassium supplements, a diet rich in potassium, or other  $\text{K}^+$ -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. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

### **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.

### **Endocrine and Metabolism**

**Gynecomastia:** Gynecomastia may develop with the use of spironolactone and physicians 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 tablets.

**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.

### **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 tablets, 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 **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 **Contraindications, Drug Interactions** section)

#### *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 adrenocorticotrophic 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.

**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 **DRUG INTERACTIONS**).

**Ophthalmologic: *Acute Myopia and Secondary Angle-Closure Glaucoma:*** Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity 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 sulphonamide 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.

**Sexual Function/Reproduction:** Spironolactone reduced fertility in female mice and increased the length of the estrous cycle in female rats (see TOXICOLOGY).

### **Miscellaneous**

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

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

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

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.

### **Special Populations**

**Pregnant Women:** see 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.

**Nursing Women:** see 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.

### **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.

## **ADVERSE REACTIONS**

The adverse reactions encountered most frequently are gynecomastia and gastrointestinal symptoms. Adverse reactions due to spironolactone and hydrochlorothiazide tablets are usually reversible upon discontinuation of the spironolactone and hydrochlorothiazide tablets. 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 WARNINGS and PRECAUTIONS-Electrolyte Balance.

*Musculoskeletal, 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 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 rash 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 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 angitis, 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 tablets are usually reversible upon discontinuation of the spironolactone and hydrochlorothiazide tablets. In rare instances, some gynecomastia may persist.

## POST-MARKET ADVERSE EVENTS

Table 1 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 and hydrochlorothiazide tablets. The causal relationship between spironolactone and hydrochlorothiazide tablets and the emergence of these events has not been clearly established.

<i>Table 1. Post-market Serious Spontaneous Adverse Event Reports</i>				
<b>Adverse Event</b>	<b>Estimated Reporting Rate</b>			
	<b>Reported Commonly ≥ 1%</b>	<b>Reported Uncommonly &lt; 1% and ≥ 0.1%</b>	<b>Reported Rarely &lt; 0.1% and ≥ 0.01%</b>	<b>Reported Very Rarely &lt; 0.01%</b>
<b>Blood and lymphatic system disorders</b>				
Thrombocytopenia				X
Agranulocytosis				X
Anaemia				X
Leukopenia				X
<b>Cardiac disorders</b>				
Bradycardia (n=2)				X
Myocardial infarction*				X
Tachycardia (n=1)				X
Arrhythmia*				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
<b>Ear and labyrinth disorders</b>				
Vertigo				X
<b>Endocrine disorders</b>				
Inappropriate ADH secretion (n=2)				X
ADH abnormality*				X
Hyperthyroidism*				X
<b>Gastrointestinal disorders</b>				
Vomiting				X
Nausea				X
Diarrhoea				X
Pancreatitis acute (necrotizing, relapsing)				X
Abdominal pain				X
Gastrointestinal haemorrhage (rectal haemorrhage)				X
Constipation				X
Melaena				X
<b>General disorders and administration site conditions</b>				
Malaise				X
Asthenia				X

Pyrexia				X
Chest pain				X
Oedema (peripheral + other)				X
Sudden death (n=1)*				X
<b>Hepatobiliary disorders</b>				
Jaundice				X
Cholestasis				X
Hepatitis*				X
Hepatomegaly*				X
Hepatic steatosis / necrosis / failure (reported 1 time each)				X

<b>Table 1. Post-market Serious Spontaneous Adverse Event Reports</b>				
<b>Adverse Event</b>	<b>Estimated Reporting Rate</b>			
	<b>Reported Commonly ≥ 1%</b>	<b>Reported Uncommonly &lt; 1% and ≥ 0.1%</b>	<b>Reported Rarely &lt; 0.1% and ≥ 0.01%</b>	<b>Reported Very Rarely &lt; 0.01%</b>
<b>Infections and infestations</b>				
Pneumonia*				X
Otitis media				X
<b>Investigations</b>				
Weight decreased*				X
Blood creatinine increased*				X
Gamma-glutamyltransferase increased*				X
Aspartate aminotransferase increased*				X
Alanine aminotransferase increased*				X
Transaminases increased*				X
Increased weight due to increased peripheral edema* (after switching to generic)				X
<b>Immune system disorders</b>				
Hypersensitivity				X
<b>Metabolism and nutrition disorders</b>				
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
<b>Musculoskeletal and connective tissue disorders</b>				
Rhabdomyolysis*				X
Myalgia, Muscular weakness				X
Systemic lupus erythematosus				
<b>Neoplasms benign, malignant and unspecified (including cysts &amp; polyps)</b>				
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
<b>Nervous system disorders</b>				
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

<b>Table 1. Post-market Serious Spontaneous Adverse Event Reports</b>				
<b>Adverse Event</b>	<b>Estimated Reporting Rate</b>			
	<b>Reported Commonly ≥ 1%</b>	<b>Reported Uncommonly &lt; 1% and ≥ 0.1%</b>	<b>Reported Rarely &lt; 0.1% and ≥ 0.01%</b>	<b>Reported Very Rarely &lt; 0.01%</b>
Brain oedema*				X
Paraesthesia				X
<b>Psychiatric disorders</b>				
Confusional state				X
Disorientation				X
Depression(n=1)				X
Aggression*				X
Agitation*				X
Abnormal behaviour*				X
Suicide attempt (n=1)*				X
<b>Renal and urinary disorders</b>				
Renal failure (acute, chronic)				X
Renal impairment				X
Tubulointerstitial nephritis*				X
Oliguria (n=1)				X
Anuria*				X
<b>Respiratory, thoracic and mediastinal disorders</b>				
Dyspnoea				X
Pulmonary fibrosis (n=1)				X
Respiratory failure*				X
Pulmonary embolism (n=1)				X
Pulmonary oedema*				X
Interstitial lung disease*				X
Cough*				X
<b>Skin and subcutaneous tissue disorders</b>				
Purpura				X
Pruritus				X
Rash maculo-papular, erythematous				X
Photosensitivity reaction				X
Dermatitis bullous*				X
Eczema*				X
Toxic epidermal necrolysis / eruption*				X
Pemphigoid*				X
<b>Vascular disorders</b>				
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 2<sup>nd</sup> quarter 1998 to 1<sup>st</sup> 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 tablets, however, they have been reported for other spironolactone/thiazide combination products (spironolactone/butizide and spironolactone/ hydroflumethiazide). n= number

## DRUG INTERACTIONS

### Drug-Drug Interactions

**Table 2. Established or Potential Drug-Drug Interactions**

Drug Interaction	Ref.	Effect	Clinical comment
<b>Alcohol, barbiturates or narcotics</b>	C	Potential of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
<b>Amphotericin B</b>	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics	Monitor serum potassium level.
<b>Antidiabetic agents (e.g. insulin and oral hypoglycemic agents)</b>	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 tablets 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.
<b>Antineoplastic drugs, including cyclophosphamide and methotrexate</b>	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.
<b>Antipyrine</b>	---	Spironolactone enhances the metabolism of antipyrine.	
<b>Atorvastatin* + furosemide + ASA</b>	---	Hepatitis, pancreatitis, death have been reported with co-treatment with spironolactone and hydrochlorothiazide tablets.	
<b>Bile acid sequestrants (e.g. Cholestyramine, Colestipol and Ammonium Chloride)</b>	CT	Bile acid sequestrants bind thiazide diuretics in the gut and impair 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.	Give thiazide 2-4 hours before or 6 hours after the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary.

Drug Interaction	Ref.	Effect	Clinical comment
<b>Calcium and vitamin D supplements</b>	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.
<b>Carbamazepine</b>	C	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution
<b>Corticosteroids, and adrenocorticotrophic hormone (ACTH)</b>	T	Intensified electrolyte depletion, particularly hypokalemia, may occur	Monitor serum potassium, and adjust medications, as required.
<b>Digoxin</b>	CT	<p>Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity.</p> <p>Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.</p>	<p>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.</p> <p>Two mechanisms of 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.</p> <p>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.</p>
<b>Diuretics and Antihypertensive Drugs</b>	CT	<p>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.</p> <p>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</p>	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 spironolactone and hydrochlorothiazide is included in the regimen.
<b>Drugs known to cause hyperkalemia +</b>	---	Concomitant use of drugs known to cause hyperkalemia with spironolactone may result in severe hyperkalemia.	



<b>Drug Interaction</b>	<b>Ref.</b>	<b>Effect</b>	<b>Clinical comment</b>
<b>Drugs that alter GI motility, i.e., anti-cholinergic agents, such as atropine and prokinetic agents, such as metoclopramide, domperidone</b>	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.
<b>Eplerenone</b>	---	Severe hyperkalemia has been associated with the use of aldosterone blockers in combination with spironolactone.	
<b>Gout medications (allopurinol, uricosurics, and xanthine oxidase inhibitors)</b>	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
<b>Heparin, low molecular weight heparin</b>	---	Concomitant use of spironolactone with heparin, low molecular weight heparin may lead to severe hyperkalemia.	
<b>Lithium*</b>	CT	Thiazide diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Co-treatment with spironolactone and hydrochlorothiazide tablets 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
<b>Norepinephrine</b>	---	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 spironolactone and hydrochlorothiazide tablets. Consideration should be given to discontinuation of spironolactone and hydrochlorothiazide tablets therapy prior to elective surgery.

Drug Interaction	Ref.	Effect	Clinical comment
<b>Non-Steroidal Anti-Inflammatory Drugs (NSAID)</b>	CT	<p>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.</p> <p>Hyperkalemia has been associated with the use of indomethacin in combination with potassium-sparing diuretics.</p> <p>NSAID-related retention of sodium and water antagonizes the diuretic and antihypertensive effects of thiazides.</p> <p>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.</p> <p>Patients with heart failure may be at particular risk.</p>	<p>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.</p> <p>If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustment may be required.</p>
<b>Selective serotonin reuptake inhibitors (SSRIs, e.g. citalopram, escitalopram, sertraline)</b>	T, C	Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
<b>Skeletal muscle relaxants of the curare family, e.g., tubocurare</b>	C	Thiazide drugs may increase the responsiveness of some skeletal muscle relaxants, such as curare derivatives.	
<b>Topiramate</b>	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

## **Drug-Food Interactions**

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 tablets are 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 Overdosage section), particularly in patients with impaired renal and hepatic function, pregnant/nursing women and elderly patients.

## **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 spironolactone and hydrochlorothiazide tablets and digoxin is necessary and safety monitoring required.

## **DOSAGE AND ADMINISTRATION**

Food effect on spironolactone and hydrochlorothiazide tablet pharmacokinetics has been observed (see Food-Drug Interaction section). 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.

**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 0.75 to 1.5 mg of spironolactone per pound of body weight (1.65 mg/kg to 3.3 mg/kg).

**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.

## OVERDOSAGE

**Symptoms:** There have been no reports of fatal overdose in man (except indirectly through hyperkalemia). Nausea and vomiting occurs, 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.

## ACTION AND CLINICAL PHARMACOLOGY

**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.

### **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.

### **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-thiomethylspironolactone, 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 ( $\pm$  SD)  $AUC_{(0-24)}$  of spironolactone increased from  $288 \pm 138$  (empty stomach) to  $493 \pm 105 \text{ ng} \cdot \text{mL}^{-1} \cdot \text{hr}$  (with food) (increase by 1.95 fold,  $p < 0.001$ ). The corresponding increases of the  $AUC_{(0-24)}$  of metabolites were 7 $\alpha$ -thiomethylspironolactone by 1.45-fold, 6 $\beta$ -hydroxy-7 $\alpha$ -thiomethylspironolactone 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- 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 5 healthy men, a single dose of spironolactone 200 mg (with radioactive tracer) was administered and in 5 days,  $31.6\% \pm 5.87\%$  of the radioactivity was excreted in the urine mainly as metabolites and  $22.7\% \pm 14.1\%$  in the feces.

**Table 3. Pharmacokinetic Parameters of Spironolactone and its Metabolites in Healthy Volunteers following the Administration of Spironolactone 100 mg daily for 15 days**

	Mean C <sub>max</sub> (ng/mL)	Mean T <sub>max</sub> (h)	Mean Post-Steady State t <sub>½</sub> (h)	Accumulation Factor: AUC <sub>0-24 h, Day 15</sub> / AUC <sub>0-24 h, Day 1</sub>
7-α-(thiomethyl) spironolactone (TMS)	391	3.2	13.8	1.25
6-β-hydroxy-7-α-(thiomethyl) spironolactone (HTMS)	125	5.1	15.0	1.50
Canrenone (C)	181	4.3	16.5	1.41
Spironolactone	80	2.6	~1.4 (t <sub>½</sub> β)	1.30

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.

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 – 4 L/kg.

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%-70% was recovered in the urine 24 hours after the oral administration of 25 mg to 65 mg of HCTZ.

## Special Populations

### 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 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 CONTRAINDICATIONS).

### Elderly

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 CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS – Hepatic/biliary/pancreatic and Renal sections).

### 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.

## STORAGE AND STABILITY

Store between 15°C to 30°C.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### 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.

Non-medicinal ingredients include: Sodium lauryl sulfate, Lactose monohydrate, Colloidal silicon dioxide, Sodium starch glycolate, Natural peppermint flavour powder, Magnesium stearate, D&C Yellow #10 AL Lake HT, FD&C Yellow #6 AL Lake HT

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.

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

Available in bottles of 100 tablets.

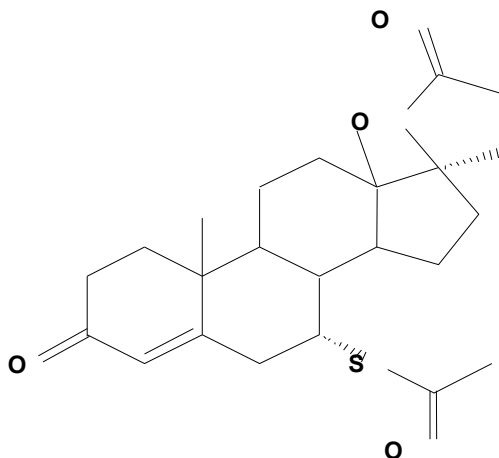


## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

A. Proper name:	Spironolactone
Chemical name:	17 $\beta$ -hydroxy-7 $\alpha$ -acetylthio-3-oxo-pregn-4-ene-21-carboxylic acid $\gamma$ -lactone
Molecular formula:	C <sub>24</sub> H <sub>32</sub> O <sub>4</sub> S
Molecular mass:	416.59 g/mol
Structural formula:	



Description:	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.
--------------	---

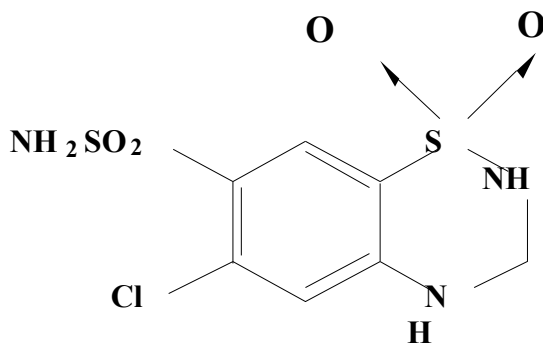
B. Proper name: Hydrochlorothiazide

Chemical name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide

Molecular formula:  $C_7H_8ClN_3O_4S_2$

Molecular mass: 297.75 g/mol

Structural formula:



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

## CLINICAL TRIALS

### **Comparative Bioavailability Study**

A single dose comparative oral bioavailability study of TEVA-SPIRONOLACTONE/HCTZ and Aldactazide tablets was carried out in 12 normal volunteers. The dose administered was 8 tablets (200 mg of spironolactone and 200 mg of hydrochlorothiazide).

A summary of the results is as follows:

<b>Spironolactone</b> <b>(8 x 25 mg spironolactone / 25 mg hydrochlorothiazide)</b> Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>0-T</sub> (ng·h/mL)	2642.7 2681.2 (17.7)	2723.5 2748.3 (14.2)	97.0	93.2-101.1
AUC <sub>0-inf</sub> (ng·h/mL)	3237.2 3294.1 (19.2)	3313.9 3348.7 (15.0)	97.7	92.7-103.0
C <sub>max</sub> (ng/mL)	242.3 246.3 (20.0)	264.49 268.4 (18.1)	91.6	84.0-99.9
T <sub>max</sub> <sup>§</sup> (h)	3.7 (24.3)	3.1 (22.6)		
T <sub>1/2</sub> <sup>ε</sup> (h)	8.6 (21.6)	8.3 (21.4)		

\* Teva-Spironolactone/HCTZ 25 mg-25 mg tablets manufactured by Teva Canada Limited., Canada

† Aldactazide® 25 mg-25 mg tablets (G.D. Searle & Co. Ltd., Canada) was purchased in Canada

§ Expressed as the arithmetic mean (CV%) only.

ε Expressed as the arithmetic mean (CV%) only.

<b>Hydrochlorothiazide</b> <b>(8 x 25 mg spironolactone / 25 mg hydrochlorothiazide)</b> Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference <sup>†</sup>	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>0-T</sub> (ng·h/mL)	6197.6 6325.0 (20.3)	6336.9 6452.0 (19.2)	97.8	94.3-101.4
AUC <sub>0-inf</sub> (ng·h/mL)	6801.1 6931.4 (19.3)	6872.5 6995.4 (19.1)	99.0	95.2-102.8
C <sub>max</sub> (ng/mL)	800.1 807.7 (14.3)	753.4 765.5 (18.9)	106.2	101.2-111.4
T <sub>max</sub> <sup>§</sup> (h)	2.5 (20.0)	3.0 (20.0)		
T <sub>1/2</sub> <sup>c</sup> (h)	5.9 (11.9)	5.8 (10.9)		

\* Teva-Spironolactone/HCTZ 25 mg-25 mg tablets manufactured by Teva Canada Limited., Canada

<sup>†</sup> Aldactazide<sup>®</sup> 25 mg-25 mg tablets (G.D. Searle & Co. Ltd., Canada) was purchased in Canada

<sup>§</sup> Expressed as the arithmetic mean (CV%) only.

<sup>c</sup> Expressed as the arithmetic mean (CV%) only.

## TOXICOLOGY

### A. Spironolactone

#### 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

Species / Number	Length of study	Dose (mg/kg/d)	Results
<b>Spironolactone</b>			
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 <b>changes</b> 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.
<b>Potassium Canrenoate</b>			
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.

### **Mutagenicity**

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.

### **Teratogenicity**

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 continuous breeding study in which female rats received dietary doses of 15 and 500 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 500 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**

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.

HCTZ was not genotoxic *in vitro* assays using bacteria (Ames assay) and mammalian cells (CHO chromosomal aberration assay), or in *in vivo* assays using mouse germ cell chromosomes, Chinese hamster bone marrow chromosomes, and the male *Drosophila* germ cells (sex-linked recessive lethal mutations). Positive test results were obtained only in the *in vitro* CHO sister chromatid exchange (clastogenicity) and in the mouse lymphoma cell (mutagenicity) assays, using concentrations of HCTZ from 43 µg/mL to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Two-year feeding studies in mice and rats uncovered no evidence of a carcinogenic potential of HCTZ in female mice at doses of up to approximately 600 mg/kg/day (15 times of the maximum recommended human dose based on body surface area) or in male and female rats at doses of up to approximately 100 mg/kg/day (5 times of the maximum recommended human dose). There was, however, equivocal evidence for hepatocarcinogenicity in male mice.

### **Teratogenicity**

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

### Long-Term Toxicity

	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.

### Teratogenicity

Spironolactone and hydrochlorothiazide tablets (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 tablets (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.



## REFERENCES

### A. Spironolactone

1. Aronoff A, Nayarai I. Le traitement de l'ascite resistant des cirrhotiques. L'Union Medical du Canada 1974; 103:2081-9.
2. Berg KJ, Gisholt K, Wideroe TE. Potassium deficiency in hypertensives treated with diuretics. Analysis of three alternative treatments by an oral test for potassium deficiency. Eur J Clin Pharmacol 1974; 7:401-5.
3. Caminos-Torres R, Ma L, Snyder PJ. Gynecomastia and semen abnormalities induced by spironolactone in normal men. J Clin Endocrinol Metab 1977; 45:255-60.
4. Eggert RC. Spironolactone diuresis in patients with cirrhosis and ascites. Br Med J 1970; 4:401-3.
5. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone. A report from the Boston Collaborative Drug Surveillance Program. J Am Med Assoc 1973; 225:40-3.
6. Karim A. Spironolactone: Disposition, metabolism, pharmacodynamics and bioavailability. Drug Metab Rev 1978; 8:151-88.
7. Kojima K, Yamamoto K, Fujioka H, Kaneko H. Pharmacokinetics of spironolactone and potassium canrenoate in humans. J Pharmacobio-Dyn 1985; 8:161-6.
8. Ouzan J, Perault C, Lincoff AM et al: The role of spironolactone in the treatment of patients with refractory hypertension. Am J Hypertens 2002; 15(4):333-339.
9. Overdiek HWPM, Hermans WAAJ, Markus FWHM. New insights into the pharmacokinetics of spironolactone. Clin Pharmacol Therap 1985; 38:469-74.
10. Wirth KE, Frolich JC, Hollifield JW, Falkner FC, Sweetman BS, Oates JA. Metabolism of digitoxin in man and its modification by spironolactone. Eur J Clin Pharmacol 1976; 9: 345-54.

### B. Hydrochlorothiazide

1. Maitland-van der Zee A, Turner S, Schwartz G, Chapman O, Boerwinkle KE. Demographic, Environmental, and Genetic Predictors of Metabolic Side Effects of Hydrochlorothiazide Treatment in Hypertensive Subjects. Am J Hypertens 2005; 18 (8): 1077-83.
2. Pashinsky VG. Toxicity of antineoplastic agents used in combination with diuretics. Farmacol Toksikol 1973; 36:605-8.
3. Peck HM. The toxicology of combinations of methyl dopa and hydrochlorothiazide. Farmaco Prat 1968; 23:241-6.

4. Pickleman JR. Thiazide-induced parathyroid stimulation. *Metabolism* 1969; 18:867-73.
5. Sheppard H. Distribution and fate of hydrochlorothiazide- $H^3$ . *Toxicol Appl Pharmacol* 1960; 2:188-94.

### **C. Spironolactone and Hydrochlorothiazide**

1. Berglund G and Andersson O. Hydrochlorothiazide and spironolactone alone and in fixed combination in hypertension. *Curr Ther Res* 1980; 27:360-4.
2. Brest AN: Spironolactone in the treatment of hypertension: a review. *Clin Ther* 1986; 8:568- 585.
3. Cocke TB. Double-blind comparison of triamterene plus hydrochlorothiazide and spironolactone plus hydrochlorothiazide in treatment of hypertension. *J Clin Pharmacol* 1977; 17:334-9.
4. Ogden DA. A comparison of the properties of chlorothiazide, spironolactone, and a combination of both as diuretic agents. *N Eng J Med* 1961; 265:358-62.
5. Settel E. Combined spironolactone – hydrochlorothiazide (ALDACTAZIDE) treatment in refractory congestive heart failure. *Curr Therapeut Res* 1961; 3:243-9.
6. Settel E. Further experience with spironolactone – hydrochlorothiazide (ALDACTAZIDE-A) in the long-term treatment of refractory cardiac edema. *J Am Geriat Society* 1965; 13:655-62.
7. Winer BM. Antihypertensive actions of diuretics. Comparative study of an aldosterone antagonist and a thiazide, alone and together. *JAMA* 1968; 204:117-21.
8. ALDACTAZIDE Product Monograph by Pfizer Canada Inc., Date of Revision: July 23, 2015, Submission Control No.: 178259

## PART III: CONSUMER INFORMATION

### TEVA-SPIRONOLACTONE/HCTZ

Spironolactone and Hydrochlorothiazide Tablets, USP

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 TEVA-SPIRONOLACTONE/HCTZ. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment, and ask if there is any new information about TEVA-SPIRONOLACTONE/HCTZ.

### ABOUT THIS MEDICATION

#### What the medication is used for:

TEVA-SPIRONOLACTONE/HCTZ is used to treat high blood pressure and fluid retention (edema) caused by various conditions, including heart disease, cirrhosis of the liver and nephrotic syndrome.

#### What it does:

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

- Spironolactone belongs to a class of medicines known as aldosterone receptor antagonists.
- Hydrochlorothiazide is a diuretic or “water pill” that increases urination. This lowers blood pressure.

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 doctor.

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.

#### When it should not be used:

Do not take TEVA-SPIRONOLACTONE/HCTZ if you:

- Are allergic to spironolactone or hydrochlorothiazide or to any non-medicinal ingredient in the formulation.
- Are allergic to sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in “-MIDE”.
- Have difficulty urinating or produce no urine.
- Have severe kidney disease, severe liver disease or Addison’s disease
- Have high levels of potassium (hyperkalemia) or calcium (hypercalcemia) in your blood.

- Are pregnant
- Are breastfeeding. Spironolactone and hydrochlorothiazide passes into breast milk
- Are taking eplerenone (INSPIRA)
- Are taking heparin or low molecular weight heparin used to prevent blood clotting

#### What the medicinal ingredient is:

Spironolactone and hydrochlorothiazide

#### What the non-medicinal ingredients are:

Sodium lauryl sulfate, Lactose monohydrate, Colloidal silicon dioxide, Sodium starch glycolate, Natural peppermint flavour powder, Magnesium stearate

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.

#### What dosage forms it comes in:

Tablets:

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

### WARNINGS AND PRECAUTIONS

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

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

Before you receive TEVA-SPIRONOLACTONE/HCTZ, talk to your doctor, nurse, or pharmacist if you:

- Are allergic to penicillin.
- Have diabetes, liver or kidney disease.
- 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 medications for diabetes
- Are taking a Non-steroidal anti-inflammatory drugs (NSAIDs) used to reduce pain and swelling. Examples include Aspirin, ibuprofen (Advil, Motrin), naproxen (Aleve), and celecoxib (Celebrex)
- 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 Lipitor (atorvastatin) or Lasix

(furosemide)

- Are pregnant, plan to become pregnant, or are breast-feeding. If you become pregnant while taking TEVA-SPIRONOLACTONE/HCTZ, call your doctor.
- Are a man and develop tender or enlarged breast tissue
- Are having surgery (including dental surgery) and will be given an anesthetic. Be sure to tell the doctor or dentist that you are taking TEVA-SPIRONOLACTONE/HCTZ.

**Hydrochlorothiazide in TEVA-SPIRONOLACTONE/HCTZ can cause Sudden Eye Disorders:**

- **Myopia:** Sudden nearsightedness or blurred vision.
- **Glaucoma:** An increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.

These eye disorders are related and can develop within hours to weeks of starting TEVA-SPIRONOLACTONE/HCTZ.

You may become sensitive to the sun while taking TEVA-SPIRONOLACTONE/HCTZ. Exposure to sunlight should be minimized until you know how you respond.

**Driving and using machines:** Before you perform tasks which may require special attention, wait until you know how you respond to TEVA-SPIRONOLACTONE/HCTZ. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is decreased (sometimes leading to falls and fractures or broken bones). Do not drive a car or operate machinery until you know how this drug affects you. Remember that alcohol can add to the drowsiness caused by this drug.

**INTERACTIONS WITH THIS MEDICATION**

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with TEVA-SPIRONOLACTONE/HCTZ:

- Adrenocorticotrophic 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, an antifungal drug.

- Anticancer drugs, including cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline.
- Antidiabetic drugs, 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.
- Drugs that slow down or speed up bowel function, including atropine, metoclopramide, and domperidone.
- Drugs used to treat epilepsy, including carbamazepine and topiramate.
- Drugs that cause hyperkalemia (high levels of potassium in blood) 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. Examples include ibuprofen, naproxen, and celecoxib.
- Other blood pressure lowering drugs, 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 tubocurarine.

**PROPER USE OF THIS MEDICATION**

Take TEVA-SPIRONOLACTONE/HCTZ exactly as prescribed by your doctor. It is recommended to take your dose at about the same time every day.

TEVA-SPIRONOLACTONE/HCTZ can be taken with or without food. If TEVA-SPIRONOLACTONE/HCTZ causes upset stomach, take it with food or milk.

**Always follow your doctor's instructions carefully.**

TEVA-SPIRONOLACTONE/HCTZ comes as a tablet to take by mouth. It is usually taken once a day in the morning.

Food increases the effect of TEVA-SPIRONOLACTONE/HCTZ. Patients with kidney and liver problems, and the elderly are particularly at risk. If you take this medication with food, your doctor must monitor you for signs that can be associated with excessive exposure of TEVA-SPIRONOLACTONE/HCTZ. Overdose symptoms include nausea, vomiting, drowsiness, dizziness,

decreased consciousness, coma, mental confusion, diarrhea, red spots/bruising/rash and irregular results on blood tests including increased serum potassium levels. These symptoms usually disappear when TEVA-SPIRONOLACTONE/HCTZ is discontinued.

### Usual Dose

**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 0.75 to 1.5 mg of spironolactone per pound of body weight (1.65 mg/kg to 3.3 mg/kg).

**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).

### Overdose

If you think you have taken too much TEVA-SPIRONOLACTONE/HCTZ contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:** If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

**Gastrointestinal:** Constipation, diarrhea, nausea, vomiting, decreased appetite, upset stomach, enlargement of the glands in your mouth, indigestion, dryness of mouth, abdominal pain, and cramps.

**Central nervous system:** Dizziness, pins and needles in your fingers, headache, a feeling that you or your surroundings are moving, sensation of tingling or numbness and drowsiness.

**Cardiovascular:** low blood pressure while you are standing (postural hypotension), may be aggravated by

alcohol, barbiturates, or narcotics.

**Hypersensitivity:** sensitivity to light, fever, difficulty breathing, anaphylactic reactions.

**Musculoskeletal:** Muscle cramps, spasms, and pain, weakness, restlessness

**Psychiatric:** Reduced libido

**Reproductive:** In men: breast swelling, difficulty in getting or maintaining erections. In women: breast discomfort, irregular or missed menstrual periods, postmenopausal bleeding.

**Skin:** Bleeding under the skin, rash, red patches on the skin.

**Other:** Blurred vision, thirst, frequent urination, and fatigue.

**If any of these affect you severely, tell your doctor, nurse or pharmacist.**

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	<b>Low Blood Pressure:</b> Dizziness, fainting, lightheadedness. May occur when you go from sitting to standing up (may be exacerbated by alcohol, barbiturates, or narcotics).	√		
	<b>Decreased levels of potassium in the blood:</b> Irregular heartbeats, muscle weakness and generally feeling unwell.		√	
Uncommon	<b>Allergic Reaction:</b> Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, redness, intense itching and burning, anaphylactic reaction.			√
	<b>Kidney Disorder:</b> Change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
	<b>Liver Disorder:</b> Yellowing of the skin		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help	
	Only if severe	In all cases		
or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite				
<b>Increased Blood Sugar:</b> Frequent urination, thirst, and hunger	✓			
<b>Electrolyte Imbalance:</b> Weakness, drowsiness, muscle pain or cramps, rapid, slow or irregular heartbeat		✓		
Confusion		✓		
Enlarged or painful breasts in men		✓		
Fever	✓			
Vomiting blood		✓		
Rapid, excessive weight loss		✓		
Shortness of breath		✓		
Skin rash		✓		
Yellowing of the skin or eyes		✓		
Stomach ulcer (burning pain in the gut, vomiting)		✓		
Blood problems (loss of energy, severe anemia).		✓		
Impaired sense of sight		✓		
Chest pain, difficulty breathing			✓	
<b>Rare</b>		✓		
<b>Decreased Platelets:</b> Bruising, bleeding, fatigue and weakness		✓		
<b>Decreased White Blood Cells:</b> Infections, fatigue, fever, aches, pains, and flu-like symptoms		✓		
<b>Very Rare</b>			✓	
<b>Toxic Epidermal Necrolysis:</b> Severe skin peeling, especially in mouth and eyes.			✓	
<b>Unknown</b>			✓	
<b>Eye Disorders:</b> <b>-Myopia:</b> Sudden near sightedness or blurred vision <b>-Glaucoma:</b> Increased pressure in your eye, eye pain			✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help	
	Only if severe	In all cases		
<b>Anemia:</b> Fatigue, loss of energy, weakness, shortness of breath		✓		
<b>Inflammation of the Pancreas:</b> Abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		✓		

*This is not a complete list of side effects. If you have any unexpected effects while taking TEVA-SPIRONOLACTONE/HCTZ, contact your doctor, nurse, or pharmacist.*

#### HOW TO STORE IT

Store between 15°C to 30°C.

**Keep out of the reach and sight of children.**

#### Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

#### 3 ways to report:

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, ON  
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

*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.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals, can be found by contacting Teva Canada Limited at:

1-800-268-4127 ext. 1255005 (**English**);  
1-877-777-9117 (**French**); or  
[druginfo@tevacanada.com](mailto:druginfo@tevacanada.com)

This leaflet was prepared by:  
Teva Canada Limited  
30 Novopharm Court  
Toronto, Ontario  
Canada  
M1B 2K9

Last revised: January 20, 2016