PACKAGE LEAFLET: Information for the patient

SPIROLAN

Tablets – 25 mg, 50 mg

(Spironolactone)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further question, ask your doctor, or pharmacist.
- This medication has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. WHAT SPIROLAN IS AND WHAT IT IS USED FOR?

Spirolan contains spironolactone as an active substance which is a diuretic drug (potassium - sparing).

Spirolan is used in:

- primary hyperaldosteronism (excessive production of a mineralocorticoid, aldosterone), if surgery is not indicated;
- accumulation of fluid in tissues and / or abdomen (oedema and / or ascites) in diseases associated with secondary hyperaldosteronism.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE SPIROLAN?

Spirolan should not be taken:

- if you are hypersensitive (allergic) to spironolactone or to any of the excipients of Spirolan;
- if there is no urine production (anuria);
- in acute renal failure;
- in serious renal impairment (renal failure with creatinine clearance below 30 ml/min for 1.73 m^2 body surface, or with serum creatinine value above 1.8 mg/dl);
- in raised content of potassium in blood (hyperkalemia);
- in sodium defficiency (hyponatremia);
- if you suffer from Addison's disease (a hormone deficiency characterised by extreme weakness, loss of weight and low blood pressure);
- if you are breastfeeding your baby.

Spirolan should not be administered concurrently with other potassium-sparing diuretics and potassium supplements should not be given routinely with it as severe hyperkalaemia may be induced.

Take special care when taking Spirolan

A careful medical surveillance is necessary in:

- mild renal impairment (serum creatinine values between 1.2 and 1.8 mg/dl or creatinine clearance between 60 ml/min, and 30 ml/min);
- patients who have a tendency to acidosis and / or hyperkalemia due to an existing illness (e.g. diabetes mellitus);
- very low blood pressure (hypotonia);
- reduced blood circulation (hypovolemia);
- acute porphyria.

During concomitant use of spironolactone and potassium-sparing diuretics, potassium substitutes or ACE-inhibitors, hyperkalemia (very high potassium levels in blood) may occur which is life-threatening. So it is not recommended to combine these drugs with spironolactone.

Treatment with Spirolan requires regular checks of serum sodium, serum potassium, serum creatinine, and acidic-basic status.

In patients with renal function impairment with serum creatinine values between 1.2 and 1.8

mg/dl or creatinine clearance below 60 ml/min for 1.73 m^2 body surface, and when using Spirolan in combination with other drugs that increase potassium levels (see paragraph 2 "Taking Spirolan with other medicines"), close medical surveillance of serum potassium levels is required.

Children

Children should not use Spirolan longer than 30 days.

Elderly

In the elderly caution is required for possible renal impairment (see paragraph 2 "Spirolan should not be taken").

The effects of misuse for doping purposes

Spirolan use can lead to positive results in doping controls.
Health consequences of Spirolan usage as doping agent can not be predicted, severe health risks can not be excluded.

Taking Spirolan with other medicines

Please tell your doctor or pharmacist if you are taking / using, have recently taken / used any other medicines, including medicines obtained without a prescription.

<u>Spirolan can be affected as follows</u>

The simultaneous administration of non-steroidal anti-inflammators (e.g. acetylsalicylic acid, indomethacin, mefenamic acid) may reduce the diuretic effect of spironolactone.
Neomycin may reduce the absorption of spironolactone.
Carbenoxolone may cause sodium retention and thus decrease the effectiveness of spironolactone; concurrent use should be avoided. Spironolactone and carbenoxolone may affect the action of each other. Large quantities of liquorice in this case act as carbenoxolone.

<u>Spirolan affects the effect of the following drugs</u>

The concomitant use of digoxin and spironolactone can lead to increased digoxin blood levels.

Spironolactone potentially increases the concentration of lithium.
Spironolactone is predicted to decrease the effects of mitotane, a medication used in the treatment of adrenocortical carcinoma. Concomitant treatment should be avoided.
Spirolan reduces your responsiveness to noradrenaline.
If you are going to have an operation where you will be given an anaesthetic, tell the doctor in charge that you are taking Spirolan.

Other possible interactions
The combination of non-steroidal anti-inflammatory drugs with spironolactone may lead to hyperkalemia.
During spironolactone use in combination with potassium salts (e.g. potassium chloride), with substances that reduce the elimination of potassium (potassium - sparing diuretics as triamterene, eplerenone or amiloride) or with ACE-inhibitors or angiotensine II receptor blockers (ARB), an increased serum potassium level to severe hyperkalemia (very high potassium level in the blood) may occur, in certain circumstances, even life-threatening (see paragraph 2 "Take special care when taking Spirolan").
Spironolactone should not be taken at the same time with potassium supplements, either in the form of medication or as a diet rich in potassium, because hyperkalaemia may appear.
During concomitant use of ACE-inhibitors, furosemide and spironolactone, acute renal failure may appear.
Spironolactone must not be used at the same time with heparin or low molecular weight heparin (medicines used to prevent blood clots) or antipyrine.
Concomitant use of spironolactone with trimethoprim and trimethoprim-sulfamethoxazole may result in clinically relevant hyperkalaemia.
Spironolactone should not be used in patients treated with tacrolimus as concomitant use can determine hyperkalemia.
Both spironolactone and ciclosporin increase potassium levels in the blood; the concomitant use of these drugs is not recommended.
When spironolactone has been used concomitantly with colestyramine (lipid-lowering medicine), hyperkaleamia in the context of hyperchloraemic metabolic acidosis has been reported.

The influence on laboratory tests

Spironolactone can influence some diagnostic tests (e.g. determination by RIAs (radioimmunological methods) of digoxin concentrations in serum).

Taking Spirolan with food and drinks

Large quantities of liquorice affect spironolactone action.

Pregnancy and breastfeeding

Consult your doctor or pharmacist before taking / using any medicine.

Pregnancy

Spirolan should not be taken during pregnancy because there is evidence that the active substance spironolactone causes hormonal imbalance in male and female offspring.

Breastfeeding

Spirolan should not be taken during breastfeeding, or breast-feeding should be stopped if use of spironolactone is essential, because the active substance or its metabolites pass in breast milk.

Driving and using machines

This drug, even if it is used as directed, can change the ability to react, thus affecting driving, using machinery or work without secure hold. This applies more in the beginning of treatment, when the dose increases and the drug is changed and also during interaction with alcohol.

3. HOW TO TAKE SPIROLAN?

Always take Spirolan as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The dosage is individual and is determined according to the illness severity and hyperaldosteronism. It should not be changed without the doctor’s recommendation.

Unless otherwise prescribed by the doctor, the usual dose is:

Adults:

- Initial dose: 1 to 2 times a day 100 mg to 200 mg spironolactone a day for 3 to 6 days.
  In case of insufficient efficacy, the daily dose can be increased up to 400 mg spironolactone per day.
- Maintenance dose: usually it starts with 50 mg to 100 mg spironolactone, till a maximal dose of 100 mg to 200 mg. The maintenance dose can be given daily, or every two to three days, according to the necessity.

Children:

- Initial dose: 3 mg spironolactone/kg of body weight every day for 5 days.
  In case of necessity, it can be increased up to 9 mg spironolactone/kg of body weight until the clinical effectiveness is achieved.
  If the treatment continues, the dose should be reduced to the minimal effective dose.

Method of administration

Take the tablets whole, with a considerable amount of liquid (preferably a glass of water [200 ml]).

Duration of use

The doctor will decide on the duration of use. It must be the shortest possible time. The need for long-term treatment should be checked regularly.

Children should not take Spirolan longer than 30 days.

Please talk to your doctor or pharmacist if you have the impression that the effect of Spirolan is too strong or too weak.

If you take more Spirolan than you should

If you suspect an overdose with Spirolan, tell your doctor immediately. Based on the symptoms, he will decide for the appropriate actions that should be taken. If symptoms are severe, immediate medical attention is needed.

Signs of an overdose

Possible signs of an overdose include: drowsiness and confusion or heart rate disorders due to the electrolytes and fluids balance disorders.

Treatment of overdose

If the drug is taken recently, it can be intended to reduce systemic absorption of the active substance through: induced vomiting, gastric lavage or administration of activated charcoal.

If you forget to take Spirolan

If you forget to take one or more doses, do not get a double dose. Continue treatment with the recommended doses.

If you stop taking Spirolan

If you stop taking the drug, in this case you may put at risk the success of the treatment.
Do not interrupt or stop earlier the treatment with Spirolan without first consulting the doctor.
If you have any further questions on the use of this medicine, ask your doctor, or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, spironolactone can cause side effects, although not everybody gets them.
For the evaluation of adverse effects the following indicators are used to show the frequency:

Very common	More than 1 in 10 users
Common	1 to 10 users out of 100
Uncommon	1 to 10 users out of 1,000
Rare	1 to 10 users out of 10,000
Very rare	less than 1 in 10,000 users
Unknown	frequency cannot be determined from the available data

Tell your doctor immediately if you experience any of the following symptoms after taking this medicine. Although they are very rare, the symptoms can be severe:

- itchiness and blistering of the skin around the lips and the rest of the body (Stevens-Johnson syndrome);

- detachment of the top layer of skin from the lower layers of skin, all over the body (toxic epidermal necrolysis);
- skin rash, fever and swelling (which could be symptoms of something more serious, drug rash with eosinophilia and systemic symptoms);
- yellowing of the skin and eyes (jaundice), spironolactone can cause impairment of liver function;
- irregular heartbeat which can be fatal, tingling sensation, paralysis (loss of muscle function) or difficulty in breathing, which may be symptoms of raised potassium levels in your blood. Your doctor will conduct regular blood tests to monitor potassium and other electrolyte levels. He / She may stop your treatment if necessary.

Other possible side effects

Very commonly, reversible breast enlargement in men (gynecomastia) has occurred. Painful swelling of the breast (mastodynia), recurrent bleeding and absence of menstruation (amenorrhea) have occurred in women. The occurrence of these side effects is dose - related. Spironolactone can cause augmentation of male-type hair (hirsutism) and deepening of the voice in women, while in men deepening of the voice and impotence.

Very commonly, especially in patients with impaired renal function, dangerous potassium increased levels (hyperkalemia) appear, which may lead to arrhythmias and paralysis (hyperkalemic paralysis).

Headache, lethargy, movement disorders (ataxia) and state of confusion may often occur:

In some cases, reduction of platelet count (thrombocytopenia) due to antibodies driven by spironolactone, eosinophilia in patients with liver cirrhosis and a pronounced decrease of some white blood cells with risk for infection and severe general symptoms (agranulocytosis) may occur.

It may appear a state of hyponatremia.

The electrolytes disorders can appear as: cardiac arrhythmias, fatigue, general muscle weakness, muscle cramps (e.g. cramps in legs) or dizziness.

An unwanted decrease in blood pressure may occur. The appearance of circulation disorders with decreased blood pressure when changing position from lying to standing (orthostatic disorder) is reported.

Spironolactone can promote or worsen blood metabolic acidosis (hyperchloremic metabolic acidosis).
It may occur a reversible increase of nitrogen-containing substances. Increased levels of uric acid are often noticed.
During treatment with spironolactone, gastrointestinal disorders (nausea, vomiting, diarrhea, gastrointestinal cramps), bleeding from the mucous membranes of the stomach and gastrointestinal ulcers may appear.
Very rarely are reported: skin rash, urticaria, anular erythema and lupus erythematosus and skin damage similar with *Lichen ruber planus*.
Pemphigoid, a condition presented with fluid-filled blisters on the skin, has been reported, but this side effect has an unknown frequency.
Very rarely are described liver adverse effects (hepatotoxicity) with increased liver enzymes and liver inflammation confirmed histologically (hepatitis) as well as bone weakness (osteomalacia) and hair loss (alopecia).
If you get any side effects, or if you notice any possible side effects not listed in this leaflet, talk to your doctor or pharmacist.

5. HOW TO STORE SPIROLAN?

Keep this medicine out of the sight and reach of children!
Do not use Spirolan after the expiry date stated on the package.
Do not store above 25ºC!
Store in the original packaging to protect it from light and humidity.

6. OTHER INFORMATION

What Spirolan contains:

The active substance is spironolactone.
Each tablet contains 25 mg or 50 mg spironolactone.
The excipients for Spirolan 25 mg and 50 mg are: maize starch, calcium hydrogen phosphate dihydrate, povidone, sodium lauryl sulphate, silica colloidal anhydrous, magnesium stearate.

Content of the packaging:

Spirolan 25 mg: carton box with 30 tablets.

Spirolan 50 mg: carton box with 30 tablets.

Marketing Authorisation Holder (MAH) and Manufacturer:

PROFARMA sh.a.,

St. “Skënder Vila”,

Tirana, Albania.

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