Aldactazine, scored tablet

Spironolactone/Altizide

Date: April 2022. Version n°10

Reference market: France

West Africa

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINALPRODUCT

ALDACTAZINE 25 mg/15 mg, scored tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Micronised Spironolactone……..……...…….25.00 mg

Altizide ……..……....15.00 mg

For a scored tablet.

Excipients with known effect: lactose and sodium (less than 1 mmol).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Scored tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Hypertension.
- Oedema of renal, cardiac and hepatic origin.

4.2. Posology and method of administration

Posology

Hypertension:

½ to 1 tablet per day. Treatment is instituted at a dosage of one half-tablet per day. If this is ineffective after 6 to 8 weeks of treatment, the dosage is increased to 1 tablet/day.

Oedema of renal and cardiac origin:

- Initial treatment: 3 to 4 tablets per day. These doses must then be lowered depending on the patient's response.
- Maintenance treatment: 1 to 2 tablets per day.

Oedema of hepatic origin:

- Initial treatment: 4 to 6 tablets per day.
- Maintenance treatment: 1 to 2 tablets per day.

In cases of oedema, these doses must be adjusted according to the response obtained (urine output, body weight) and the patient's electrolyte balance.

4.3. Contraindications

This drug MUST NEVER be used in cases of:

- Acute or severe renal failure and in particular: anuria, severe progressive renal disease,
- Addison's disease,
- Hyperkaliemia,
- Terminal stage of hepatic insufficiency,
- Hypersensitivity to spironolactone, sulfonamides or to one of the excipients listed in section 6.1,
- Combination with other potassium-sparing diuretics (alone or combined) such as: amiloride, potassium canrenoate, eplerenone, triamterene unless there is hypokaliemia (see section 4.5),
- Combination with mitotane (see section 4.5),
- Significant hypercalcemia.

4.4. Special warnings and precautions for use

Special warning

Combination of a potassium sparing diuretic and a natriuretic does not rule out the occurrence of hyperkaliemia or hypokaliemia.

Hypokaliemia

The risk of occurrence of hypokaliemia (< 3.5 mmol/l) must be prevented in certain high-risk population such as elderly and/or malnourished and/or polymedicated cirrhotic patients with oedema and ascites coronary artery disease and cardiac failure patients. In this situation hypokaliemia increases the cardiac toxicity of digitalis preparations and the risk of rhythm disorders.
Individuals with a prolonged QT interval are also at risk whether this is of congenital or iatrogenic origin. Hypokaliemia (and bradycardia) is then a predisposing factor to the onset of arrhythmias (in particular potentially fatal *torsades de pointes).*

Monitor serum potassium levels when using concomitantly with other drugs known to increase the risk of hypokaliemia induced by thiazide diuretics.

Hyperkaliemia

Concomitant use of medicinal products known to cause hyperkaliemia with altizide/spironolactone may result in severe hyperkaliemia.

Any prescription of a medicine acting on the renin-angiotensin-aldosterone system is likely to cause hyperkalemia. This risk, potentially fatal, is increased in elderly patients, or with renal failure or diabetes, and/or if in case of combination of several drugs and/or upon the occurrence of intercurrent events (see also section 4.5).

Before considering a combination of several drugs that block the renin-angiotensin-aldosterone system, we must carefully evaluate the benefit/risk balance and the existence of possible alternatives.

The mains risk factors for hyperkaliemia to consider are:

- diabetes, impaired renal function, age (> 70 years) and affections known to cause hyperkaliemia;
- combination with one or more other drugs blocking the renin-angiotensin-aldosterone and/or other potassium sparing drugs and/or potassium supplements and a diet rich in potassium. Some drugs or therapeutic classes are indeed likely to increase the risk of severe hyperkaliemia in association with spironolactone: potassium salts, diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists (ARAII), anti-inflammatory NSAIDs (including selective inhibitors of COX 2), heparin (low molecular weight or unfractionated), immunosuppressant such as cyclosporine or tacrolimus, trimethoprim or other drugs known to cause hyperkaliemia.
- intercurrent events, particularly dehydration, congestive heart failure, metabolic acidosis, impaired renal function, sudden and significant deterioration of general condition (e.g., during infectious disease), cell suffering and lysis (e.g., acute ischemia of a member, rhabdomyolysis, extended trauma).

Monitoring of patients, including patients at risk should include a blood ionogram, especially with control of serum potassium, serum sodium, and kidney function:

- before initiation of therapy and a week to 15 days after,
- as well (before and after) each increase of dose or treatment change.

Then in maintenance therapy, the controls should be performed regularly or at occurrence of an intercurrent event.

Risk of hepatic encephalopathy when liver function is impaired in particular when serum sodium levels are below 125 mmol/l and in subjects liable to present acidosis. Administration of this diuretic combination must be stopped immediately if this occurs.

Cases of photosensitivity reaction have been reported with the use of thiazide diuretics (see section 4.8).

In case of occurrence of photosensitivity reaction during treatment, it is recommended to discontinue the treatment. If a challenge is required, it is recommended to protect areas exposed to sunlight or artificial UVA.

The attention of athletes is drawn to the fact that this drug contains an active substance that may give a positive reaction in doping tests.

Choroidal effusion, acute myopia and acute closed-angle glaucoma

Hydrochlorothiazide, a sulfonamide, has been associated to an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute closed-angle glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. In the absence of treatment, closed-angle 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. The history of sulfonamide or penicillin allergy is a risk factor for developing acute closed-angle glaucoma.

Excipients

This medicine contains lactose. Patients with rare heredity problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption syndrome (rare hereditary diseases) should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Precautions for use

Water and electrolyte balance

- Serum sodium

This must be measured before starting treatment and then subsequently at regular intervals in particular in elderly subjects and in cirrhotic patients in whom administration is not recommended when serum sodium levels are below 125 mmol/l.

- Serum calcium

Thiazide and related diuretics reduce urinary calcium excretion and can cause a slight and transient rise in serum calcium in the absence of known abnormalities of calcium metabolism. ALDACTAZINE should be used with caution in patients with hypercalcemia and should be administered only after correction of any pre-existing hypercalcemia. ALDACTAZINE should be discontinued in case of occurrence of hypercalcemia during treatment. Serum calcium levels should be monitored regularly during treatment with thiazide diuretics. Marked hypercalcemia may be the sign of hidden hyperparathyroidism. Thiazides diuretics should be discontinued before investigating parathyroid function.

- Uric acid

There may be an increase in the tendency to gout attacks in gout or hyperuricemic patients.

Renal function

Spironolactone and altizide are only fully effective when renal function is normal or only minimally impaired (serum creatinine less than values of approximately 25 mg/l or 220 µmol/l in an adult).

The serum creatinine value may be falsely reassuring about renal function which may be better evaluated from blood electrolytes or a formula such as Cockcroft's formula which takes into account age, body weight and sex:

Cl_{cr} = (140 - age) x body weight/0.814 x serum creatinine

- With age is given in years,
- Body weight in kg,
- Serum creatinine in micromol/l.

This formula is valid for male subjects, and for females the result must be multiplied by 0.85.

Hypovolemia secondary to the loss of water and sodium induced by the diuretic at the start of treatment causes a reduction in glomerular filtration. This may lead to an increase in blood urea and serum creatinine. This transient functional impairment in renal function is of no consequence in individuals with normal renal function though it may worsen preexisting renal insufficiency.

Anaesthesia

Caution during anaesthesia: sensitivity to norephedrin may be reduced and that to tubocurarine may be increased.

4.5. Interaction with other medicinal products and other forms of interaction

RELATED TO SPIRONOLACTONE

Certain drugs or therapeutic classes may promote the occurrence of hyperkaliemia. Potassium salts, hyperkaliemic diuretics, angiotensin-converting enzyme inhibitors, angiotensin II antagonists,

nonsteroidal anti-inflammatory drugs, heparins (low molecular weight or unfractionated), immunosuppressive such as cyclosporine or tacrolimus, trimethoprim.
Combination of these drugs increases the risk of hyperkaliemia. This risk is particularly important with potassium-sparing diuretics, especially when combined together or with salts of potassium, whereas the combination of an ACE inhibitor and an NSAID, for example, is safer when currently recommended precautions are implemented.
For information on risks and levels of constraints specific to potassium sparing drugs, it should refer to the interaction of each substance. Some substances are not subject to specific interactions with regard to this risk. However, they may act as predisposing factors when combined with other drugs already mentioned in this heading.

In addition to other medicinal products known to cause hyperkaliemia concomitant use of trimethoprim/sulfamethoxazole (co-trimoxazole) with altizide/spironolactone may result in clinically relevant hyperkaliemia.

Contraindicated combinations

+ **Other Potassium-sparing diuretics (alone or in combination) (amiloride, potassium canrenoate, eplerenone, triamterene)**

Potentially fatal hyperkaliemia in particular in patients with impaired renal function (potentiation of hyperkaliemic effects).

Contraindicated except where hypokaliemia exists.

+ Mitotane

Risk of blocking the action of mitotane by spironolactone.

Unadvisable combinations

+ Abiraterone

Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels in abiraterone-treated prostate cancer patients.

Use with abiraterone is not recommended.

+ Potassium

For a quantity of potassium > 1 mmol/dose, potentially fatal hyperkaliemia in particular in patients with impaired renal function (potentiation of hyperkaliemic effects).

Combination not recommended unless with hypokaliemia.

+ **Cyclosporine, tacrolimus**

Potentially fatal hyperkaliemia in particular in patients with impaired renal function (potentiation of hyperkaliemic effects).

+ **Angiotensin-converting enzyme inhibitors**, **angiotensin II receptor antagonist inhibitors**

Except for spironolactone at doses between 12.5 mg and 50 mg per day in the treatment of cardiac failure and in case of hypokaliemia:

Potentially fatal hyperkaliemia in particular in patients with impaired renal function (potentiation of hyperkaliemic effects).

If the combination is justified, kaliemia and renal function must be strictly monitored.

Combinations requiring precautions for use

+ **Angiotensin-converting enzyme inhibitors**

With spironolactone at a dose range from 12.5 mg to 50 mg daily, and with low doses of ACE inhibitors.

In the treatment of heart failure stage III or IV (NYHA) with an ejection fraction < 35% and previously treated with an ACE inhibitor + loop diuretic combination: Risk of potentially fatal hyperkaliemia in the event of non-compliance with the prescribing conditions for the combination.

Check the absence of hyperkaliemia and renal insufficiency. Close laboratory monitoring of serum potassium and creatinine (once weekly during the first month and then once a month).

+ Hypokaliemic diuretics

A rational combination, useful for some patients, does not mean that hypokaliemia cannot occur or, in particular with renal impairment and diabetes, hyperkaliemia.

Monitor the potassium levels, if necessary ECG and if necessary review the treatment.

Combinations to be taken into account

+ **Other hyperkaliemic drugs**

Increase of the risk of potentially fatal hyperkaliemia.

RELATED TO ALTIZIDE

+ Hyponatremiant drugs

Some drugs are more frequently involved in the occurrence of hyponatremia. These are diuretics, desmopressin, antidepressants inhibiting serotonin reuptake, carbamazepine and oxcarbazepine. The combination of these drugs increases the risk of hyponatremia.

Combinations requiring precautions for use

+ **Other hypokaliemics**

Increased risk of hypokaliemia.

Monitor the potassium levels and adjust if necessary.

+ **Digitalis preparations**

Hypokaliemia predisposes to the toxic effects of digitalis.

Correct any hypokaliemia first of all and carry out clinical, electrolytic and electrocardiogram monitoring.

+ Medicines likely to induce torsades de pointes

Increased risk of ventricular rhythm disorders, particularly torsades de pointes.

Correct any hypokaliemia before administering the product and carry out clinical, electrolytic and electrocardiogram monitoring.

+ **Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists**

Sudden hypotension and/or acute renal failure may occur after institution or increase in the dosage of an ACE inhibitor or angiotensin II antagonist in the presence of preexisting sodium depletion (in particular in patients with renal artery stenosis).

In hypertension: When prior diuretic treatment could have caused sodium depletion, it is necessary:

- either to discontinue the diuretic before starting treatment with the ACE or angiotensin II antagonist and restart a hypokaliemic diuretic later if necessary;
- or give low initial doses of the ACE inhibitor or angiotensin II antagonist and gradually increase the dosage.

In congestive heart failure treated with diuretics (only concerns combination with ACE inhibitor): start with a very low dose of ACE inhibitor, possibly after reduction in the dose of the concomitant hypokaliemic diuretic.

In every case: monitor renal function (serum creatinine) during the first weeks of treatment with ACE or angiotensin II antagonist.

+ Carbamazepine

Risk of symptomatic hyponatremia

Clinical and biological monitoring. If possible use another type of diuretic.

+ Potassium-saving diuretics (alone and in combination)

The rational association, useful for some patients, does not mean that hypokaliemia may not occur or, in particular in patients with renal impairment and diabetes, hyperkaliemia.

Monitor potassium levels, if necessary perform an ECG and, if necessary, review the treatment.

+ Antidiabetics (oral hypoglycemic agents and insulin)

Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance.

Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required (see section 4.4).

Combinations to be taken into account

+ **Calcium**

Risk of hypercalcemia due to reduced urinary elimination of calcium.

+ **Cyclosporine**

Risk of increased serum creatinine levels without any change in circulating cyclosporine levels even in the absence of water/sodium depletion. Also, risk of hyperuricemia and complications, such as gout.

RELATED TO THE COMBINATION

Inadvisable combinations

+ Lithium

Increased serum lithium with signs of overdose in lithium, as during a sodium-free diet (reduced urinary lithium excretion).

If the combination cannot be avoided, strict monitoring of serum lithium with adjustment of the dosage.

Combinations requiring precautions for use

+ **Nonsteroidal anti-inflammatory drug**

Acute renal failure in at-risk patients (elderly, dehydrated, on diuretics, with impaired renal function) by a decrease in glomerular filtration, secondary to a decrease in synthesis of renal prostaglandins. These effects are generally reversible. Additionally, reduction of the antihypertensive effect.

Administer fluids and monitor renal function at the start of treatment and regularly during the combination.

+ **Acetylsalicylic acid**

At anti-inflammatory doses of acetylsalicylic acid (≥ 1 g per dose and/or ≥ 3 g per day) or for analgesic or antipyretic doses (≥ 500 mg per dose and/or <3 g per day)):

Acute renal failure at-risk patients (elderly, dehydrated, on diuretics, with impaired renal function) by a decrease in glomerular filtration, secondary to a decrease in synthesis of renal prostaglandins. Additionally, reduction of the antihypertensive effect.

Administer fluids and monitor renal function at the start of treatment and regularly during the combination.

+ **Metformin**

Metformin induced lactic acidosis due to possible functional renal failure associated with diuretics and in particular loop diuretics.

Do not use metformin when serum creatinine exceeds 15 mg/litre (135 µmol/litre) in men and 12 mg/litre (110 µmol/litre) in women.

+ **Iodinated contrast agents**

In the presence of dehydration caused by diuretics there is an increased risk of acute renal function failure in particular when large doses of contrast agents are used. Rehydration before administration of the iodinated compound.

+ Digoxin

Spironolactone has been shown to increase the half-life of digoxin.

Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events (see section 4.4).

Combinations to be taken in account

+ **Corticosteroids**

Decreased antihypertensive effect (water/salt retention due to corticosteroids).

+ **Urological alpha-blockers**

Enhanced hypotensive effect, enhanced risk of orthostatic hypotension.

+ **Antihypertensive alpha-blockers**

Enhanced hypotensive effect, enhanced risk of orthostatic hypotension.

+ Other hyponatremic medicines

Increased risk of hyponatremia

+ Drugs causing orthostatic hypotension

Additionally to antihypertensive drugs, many drugs can cause orthostatic hypotension. This is the case of nitrates and related, type 5 phosphodiesterase inhibitors, alpha blockers for urological use, imipramine antidepressants and phenothiazine neuroleptics, dopamine agonists, levodopa, baclofen, amifostine.

Increased risk of hypotension, including orthostatic.

4.6. Fertility, pregnancy and lactation

Pregnancy

The administration of this product is not recommended during pregnancy and should be reserved only for indications where there is no therapeutic alternative.

Diuretics can cause foetoplacental ischemia with a risk of impaired foetal growth.

Effects related to spironolactone

Studies in experimental animals have failed to demonstrate any teratogenic effect. However at high doses, feminisation of male foetuses was observed after spironolactone administration throughout foetal life that is after organogenesis.

The risk is not known in clinical medicine. However, no feminisation of a male foetus has been reported to date.

In the absence of clinical data, the use of spironolactone should be avoided in pregnant women and it should be reserved for indications where there is no therapeutic alternative.

In particular, treatment of oedema, water/sodium retention of hypertension of pregnancy are not an indication for treatment with diuretics during pregnancy as these may cause foetoplacental ischemia with a risk of impaired foetal growth.

Effects related to altizide

Studies in animals are insufficient.

Thiazides cross the placental barrier.

There is limited experience with thiazides during pregnancy, especially during the first trimester. Based on the pharmacological mechanism of action of thiazides the use of altizide during the second and third trimesters can decrease the foeto-placental perfusion and cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Thiazides should not be used for gestational oedema, 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.

Diuretics nevertheless remain an essential component of the treatment of oedema or cardiac, hepatic and renal origin occurring in pregnant women.

Lactation

ALDACTAZINE should not be used during breastfeeding.

Effects related to spironolactone

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

Spironolactone is excreted in small quantities into the maternal milk.

Nevertheless it should not be used by breastfeeding mothers because of the:

- Reduction or even suppression of lacteal secretion.
- Adverse effects in particular on laboratory parameters (serum potassium).

Effects related to altizide

Thiazide diuretics are excreted in small quantities into the maternal milk. Nevertheless they are not recommended during breastfeeding period because of the:

- Severe diuresis effect which could lead to suppression of lacteal secretion when they are administered in high doses.
- Adverse effects in particular on laboratory parameters (serum potassium).

Their relation to sulfonamide with the risk of allergy and nuclear jaundice.

Fertility

Effects related to spironolactone

Spironolactone administered to female rodent reduced fertility.

4.7. Effects on the ability to drive and use machines

Not applicable.

4.8. Undesirable effects

RELATED TO SPIRONOLACTONE

These adverse effects have been observed in adults:

Clinically

A gynecomastia may occur during the use of spironolactone: Its development seems to be related both to the dosage used and to the duration of therapy. It is usually reversible on discontinuation of spironolactone administration though it may persist in a few rare cases.

Other rare adverse effects which are usually reversible at the end of spironolactone treatment have been observed, including:

- Gastrointestinal disorders: gastro-intestinal intolerance.
- Hepatobiliary disorders: hepatitis.
- Musculoskeletal and connective tissue disorders: cramps in the lower limbs.
- Nervous system disorders: drowsiness.
- Reproductive system and breast disorders: menstruation disorders in women, impotence in males.
- Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS syndrome), skin rash, pemphigoid.
- Renal and urinary disorders: acute renal failure.

Laboratory parameters

Electrolyte disturbance and hyponatremia can be observed.

Spironolactone may cause a moderate rise in serum potassium levels. More marked hyperkaliemia has been reported in patients with renal failure, those receiving potassium supplements or ACE inhibitors. Although these cases of hyperkaliemia are nearly always asymptomatic they must be rapidly corrected. Spironolactone treatment must be discontinued in the case of hyperkaliemia (see section 4.4).

RELATED TO ALTIZIDE

The majority of adverse effects concerning clinical or laboratory parameters are reversible and may be reduced by finding the minimum effective dose in particular in hypertension.

Thiazide-related diuretics may cause:

Laboratory parameters

- Potassium depletion with hypokaliemia in particular in the presence of intense diuresis and particularly serious in certain high-risk populations (See section 4.4).

- Hyponatremia with hypovolemia responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: The incidence and degree of this effect are slight.
- Increase in serum uric acid and blood glucose during treatment; the appropriateness of these diuretics must be very carefully weighed in patients with gout and diabetes.
- Hematological disorders and much rarely, thrombocytopenia, leukopenia, agranulocytosis, medullary aplasia, haemolytic anemia.
- Very rare: hypercalcemia.

Clinically

- In case of hepatic insufficiency, possible onset of hepatic encephalopathy (see sections 4.3 and 4.4).
- Hypersensitivity reactions, mainly dermatological in subjects with a predisposition to allergic and asthmatic reactions.
- Cases of photosensitivity reaction (uncommon) have been reported (see section 4.4).
- Maculopapular rashes, purpura, possible worsening of pre-existing disseminated acute lupus erythematosus;
- Rarely and usually disappearing after a reduction in the dosage: nausea, constipation, vertigo, asthenia, paresthesias, headaches.
- Very rare: pancreatitis.
- Eye disorders: acute closed-angle glaucoma (see section 4.4).

Description of selected adverse reactions:

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any adverse reactions via the national reporting system.

4.9. Overdose

The signs of acute poisoning take the form above all of water/electrolyte disturbances (hyponatremia, hypokaliemia).

Clinically, nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria to the point of anuria (by hypovolemia) may occur.

Initial measures involve the rapid elimination of the ingested substance(s) by gastric wash-out and/or administration of activated charcoal followed by restoration of the water/electrolyte balance to normal in a specialized centre.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: thiazide diuretics and potassium-sparing diuretics in combination, ATC code: C03EA04: cardiovascular system.

Mechanism of action

The combination of altizide (thiazide diuretic) and spironolactone (potassium-sparing diuretic with an anti-hormone action) gives a low natriuresis with a potassium sparing effect thereby reducing the loss of potassium induced by altizide.

Altizide acts by inhibiting reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium thereby increasing urine output and has an antihypertensive action.

Spironolactone is a competitive antagonist of aldosterone at the level of mineralocorticoid hormone receptors.

By blocking sodium potassium exchange at the level of the distal bypass tubule, it reduces the reabsorption of sodium ions and the excretion of potassium ions.

5.2. Pharmacokinetic properties

Absorption

Spironolactone

Spironolactone is absorbed by the gastrointestinal tract.

Following oral administration of 500 mg tritiated spironolactone in five healthy male volunteers (fasting state), the total radioactivity in plasma reached a peak between 25 and 40 minutes. Following single dose oral administration of 1 or 2 tablets of a fixed combination of spironolactone (25 mg) and altizide (15 mg), the maximum plasma concentrations for spironolactone were reached at approximately 1,2 hours.

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.

Administration with food resulted in higher exposure compared with fasting conditions. Following a single oral dose of 200 mg spironolactone to four healthy volunteers, the mean (± SD) AUC (0 to 24 hours) of the parent drug increased from 288 ± 138 (empty stomach) to 493 ± 105 ng ml^{-1} h (with food) ($p < 0.001$).

Altizide

Following single dose oral administration of 1 or 2 tablets of a fixed combination of spironolactone (25 mg) and altizide (15 mg), altizide is rapidly absorbed by the gastrointestinal tract and its maximum plasma concentrations were reached at approximately 2,5 hours.

Distribution

Spironolactone

Approximately 90% of spironolactone was protein bound based on equilibrium dialysis. Spironolactone or its metabolites can cross the placental barrier or appear in breast milk.

Altizide

No pharmacokinetic studies have been performed with altizide in protein binding. Altizide can cross the placental barrier or appear in breast milk.

Biotransformation

Spironolactone

Spironolactone is metabolised by both the kidneys and liver. Following deacetylation and S-methylation, spironolactone is converted to 7-α-thiomethylspironolactone, a sulfur-containing active metabolite which is considered the major metabolite of spironolactone in serum. Approximately 25% to 30% of spironolactone is also converted to canrenone by dethioacetylation (non-sulphur containing active metabolite).

Altizide

The metabolism of altizide is related to that of thiazide diuretics.

Elimination

Spironolactone

In one pharmacokinetic study in five healthy male volunteers receiving 500 mg of spironolactone, 47% to 57% of the dose was excreted in the urine within 6 days and the remaining amount could be detected in the feces (total recovery 90%). In another study of five healthy men, a single dose of spironolactone 200 mg (with radioactive tracer) was administered and in 5 days, 31.6% ± 5.87% of the radioactivity was excreted in the urine mainly as metabolites and 22.7% ± 14.1% in the faeces. Following oral administration of 1 or 2 tablets of a fixed combination of spironolactone (25 mg) and altizide (15 mg), the elimination half-life mean values for spironolactone were 0.71 to 0.86 hours.

The main urinary metabolites are:

- Canrenone (or aldadiene),
- The glucoronide ester of canrenoate,

- The 6-β-OH sulfoxide,
- The 6-β-OH thiomethyl derivative,
- 15-α hydroxycanrenone.

The peak anti-mineralocorticoid effect of spironolactone is obtained after 24 hours and its diuretic effect lasts for 24 to 48 hours.

Altizide

Altizide is excreted by the kidneys. Following single dose oral administration of 1 or 2 tablets of a fixed combination of spironolactone (25 mg) and altizide (15 mg), the elimination half-life mean values for altizide were 2,36 to 2,38 hours.

Special Populations

No pharmacokinetic studies have been performed with spironolactone/altizide in the elderly or pediatric population or in patients with hepatic or renal insufficiency.

5.3. Preclinical safety data

Spironolactone is partially transformed in the body into canrenone or aldadiene and numerous metabolites the most active of which are unchanged spironolactone, 7-α thiospironolactone and 7-α-thiomethylspironolactone.

Mutagenicity tests gave discordant results.

Certain carcinogenicity studies on canrenone have showed the existence of abnormalities though it was impossible to extrapolate these results to humans. Studies conducted with spironolactone were negative.

In rats, oral administration of spironolactone for 18 months induced an increased incidence of thyroid follicular cell adenomas and tumors of Leydig cells. The clinical relevance of these lesions is not known.

In mice, spironolactone induced a decrease of fertility in female by inhibiting ovulation and implantation. In rats, disruption of estrous cycle was observed. The effects on male fertility have not been the subject of a specific study.

No effect was reported on embryo-fetal development in mice treated with doses less than the equivalent dose to the maximum recommended dose. In rats, an increase in fetal mortality was observed after daily administration of a dose equivalent to 25 times the maximum recommended dose. Feminization of male fetuses was reported after daily administration of a dose equivalent to 10 times the maximum recommended dose, probably linked to the known anti-androgenic activity of spironolactone. Another study showed that prenatal exposure to spironolactone induced in male rats and female effects on the male reproductive system (decreased weight of the prostate and seminal vesicles) and female (weight increase of the ovaries and the uterus) persisting into adulthood. In rabbits, increased resorption was observed after daily administration of a dose equivalent to 2 times the maximum recommended dose.

The administration of spironolactone to sexually immature female rats induced delayed puberty.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Rice starch, lactose monohydrate, magnesium stearate, potassium polymethacrylate, sodium lauryl sulfate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

18 months.

6.4. Special precautions for storage

Store at a temperature not exceeding 25°C.

6.5. Nature and contents of container

20 tablets in blister (PVC/aluminium).

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Holder:
PFIZER HOLDING FRANCE
23-25, AVENUE DU DOCTEUR LANNELONGUE
75014 PARIS

Manufacturer :
PHARMACIA SAS
1, RUE ANTOINE LAVOISIER
78280 GYANCOURT

or

PIRAMAL HEALTHCARE UK LIMITED
WHALTON ROAD - MORPETH
NORTHUMBERLAND
NE61 3YA
UNITED KINGDOM

or

DELPHARM EVREUX
5 RUE DU GUESCLIN
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Local representative:
Pfizer Afrique De L'Ouest

Administrative address:
PFIZER AFRIQUE DE L'OUEST
REGUS PLATEAU 3RD FLOOR
AZUR 15 BUILDING
12 BOULEVARD DJILY MBAYE
DAKAR SÉNÉGAL BP 3857 DAKAR RP

8. GENERAL CLASSIFICATION FOR SUPPLY

List II.

9. DATE OF REVISION OF THE TEXT

24th March 2022.