1. INDICATIONS AND USAGE

CAROSPIR is indicated for treatment of NYHA Class III-IV heart failure and reduced ejection fraction to increase survival, manage edema, and to reduce the need for hospitalization for heart failure.

CAROSPIR is usually administered in conjunction with other heart failure therapies.

2. DOSAGE AND ADMINISTRATION

The recommended dose of CAROSPIR for the treatment of heart failure is 200 mg/day (4 mL) in adults. The dose may be increased as needed, based on response, up to 400 mg (8 mL) once daily. Doses above 400 mg (8 mL) once daily are not recommended because they do not provide a proportional increase in blood pressure and may increase the risk of adverse events.

3. CONTRAINDICATIONS

CAROSPIR is contraindicated in patients with the following conditions:

- Impaired neurological function/coma in patients with hepatic impairment, cirrhosis, or severe hepatic disease.
- Hypersensitivity to spironolactone or any of its excipients.
- Pregnancy.

4. WARNINGS AND PRECAUTIONS

4.1 Hypertension

4.2 Heart Failure

4.3 Electrolyte and Metabolic Abnormalities

4.4 Gynecomastia

5. ADVERSE REACTIONS

5.1 Hypotension and Worsening Renal Function

5.2 Hypertension and Worsening Renal Function

5.3 Electrolyte and Metabolic Abnormalities

5.4 Gynecomastia

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

6.2 Lactation

6.3 Children

6.4 geriatric use

6.5 Renal Impairment

6.6 Hepatic Impairment

6.7 Use in Caring for Pregnant Women

7. DRUG INTERACTIONS

7.1 Drugs That Increase Renal Clearance

7.2 Drugs That Decrease Renal Clearance

7.3 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

7.4 Digoxin

7.5 Cholestyramine

7.6 Acetylsalicylic Acid

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Children

8.4 Geriatric Use

8.5 Renal Impairment

8.6 Hepatic Impairment

8.7 Pregnancy Category

9. NONCLINICAL TOXICOLOGY

9.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

9.2 Pregnancy Category

9.3 Toxicology Summary

10. CLINICAL STUDIES

11. DESCRIPTION

12. CLINICAL PHARMACOLOGY

13. CLINICAL PHARMACOLOGY

14. CLINICAL PHARMACOLOGY

15. CLINICAL PHARMACOLOGY

16. HOW SUPPLIED/STORAGE AND HANDLING

17. PATIENT COUNSELING INFORMATION

18. CLINICAL STUDIES

19. CLINICAL STUDIES

20. CLINICAL STUDIES

21. CLINICAL STUDIES

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renal tubule. Spironolactone causes increased amounts of sodium and water to be excreted, while potassium is retained. Spironolactone acts both as a diuretic and as an antihypertensive agent. The mechanism of action is given alone or with other diuretic agents that act more proximally in the renal tubule.

12.2 Pharmacodynamics

Aldosterone antagonism: Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism. Stated differences in which secondary aldosteronism includes canrenone with hyperparathyroid, hyperplasia, cirrhosis, and nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone reduces the effects of aldosterone in the distal tubule, and has been shown to induce diuresis and sodium excretion. Spironolactone counteracts secondary aldosteronism reduced by the volume depletion and hypokalemia due to chronic diuretic therapy and by diuretic therapy. Spironolactone agrees in studies comparing the suspension to tablets, doses of suspension higher than 100 mg might result in spironolactone concentrations that could be higher than expected.

Absorption

The peak plasma concentration (Cmax) of spironolactone is reached 0.5 to 1.5 hours after dosing. In healthy volunteers, the absolute bioavailability of the active canine metabolite, the Cmax of spironolactone 25 mg of suspension is 27 nmol/L reached around 2.5 to 5 hours after dosing.

Effect of food: A high fat and high calorie meal (57% of the ~1000 kcal of the meal from fat) increased the bioavailability of spironolactone (as measured by AUC) by approximately 91%. Patients should establish a routine pattern for taking CAROSPIR with regard to meals (see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)

Distribution and Metabolism

Spironolactone is rapidly and extensively metabolized. Metabolites can be divided into two main components, those in which the sulfinyl group of the parent molecule is preserved (e.g., canrenone) and those in which the sulfinyl group is retained (e.g., TMS and TMTS). In humans, the principal metabolic pathway involves oxidation of the synthetic mineralocorticoid, spironolactone, on urinary electrolyte composition and antihypertensive effect. Spironolactone (100 mg/kg/day), administered i.p. to female mice during a two-week precoital observation period with untreated males, decreased the number of males that fathered offspring and led to an inhibition of implantation and the increased number of imposter embryos in those that became pregnant (effect shown to be caused by an inhibition of implantation), and at 200 mg/kg, increased the latency to mating.

14 CLINICAL STUDIES

14.1 Heart Failure

The Randomized Aldactone Evaluation Study (RALES) was a placebo-controlled, double-blind study of the effect of spironolactone on mortality in New York Heart Association (NYHA) class III and IV heart failure patients with a history of NYHA class IV symptoms. To be eligible to participate, patients had to have an ejection fraction of 35% or less, NYHA class III or IV symptoms, and a history of NYHA class IV symptoms in the last 6 months before enrollment. Patients with a baseline serum creatinine of 2 or 2.5 mg/dl, or a recent increase in serum creatinine of 0.5 mg/dl, were excluded. Forced convection and laboratory measurements (including serum potassium and creatinine) were performed every four weeks for the first 2 weeks, then every 3 months for the first year, and then every 6 months thereafter. The RALES study was conducted with a formulation of spironolactone that is not therapeutically equivalent to CAROSPIR (see Dosage and Administration (2.2) and Clinical Pharmacology (12.2). The initial dose of spironolactone was 25-mg once daily. Patients who were intolerant of the initial dosage regimen had their dose decreased to 12.5 mg once daily, then 10 mg once daily, and finally 7.5 mg once daily. Patients who could not tolerate the dose of 7.5 mg once daily had their dose lowered to 6.25 mg once daily.

15 MANUFACTURING INFORMATION

The RALES study was conducted with a formulation of spironolactone that is not therapeutically equivalent to CAROSPIR (see Dosage and Administration (2.2) and Clinical Pharmacology (12.2). The initial dose of spironolactone was 25-mg once daily. Patients who were intolerant of the initial dosage regimen had their dose decreased to 12.5 mg once daily, then 10 mg once daily, and finally 7.5 mg once daily. Patients who could not tolerate the dose of 7.5 mg once daily had their dose lowered to 6.25 mg once daily.

16 HOW SUPPLIED/STORAGE AND HANDLING

CAROSPIR (spironolactone) Oral Suspension 25 mg/5 mL is a white to off-white, opaque, banana-flavored suspension. It is available in a 118 mL bottle (NDC 46287-021-04) and a 473 mL bottle (NDC 46287-020-20). Store at 20°C to 25°C (68°F to 77°F). Excepts permitted to 10°C (50°F to 68°F) (see US-FDA Control Room Temperature). Shake well before use. Dispense in a light tight container as defined in the USP.

17 PATIENT COUNSELING INFORMATION

• Advise patients to take CAROSPIR consistently with respect to food.

• Advise patients to avoid potassium supplements and foods high in potassium.

• Advise patients to avoid use of laevorotatory (L) spironolactone.

• Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use two forms of non-hormonal contraception for at least 28 days after the last dose of a presumed or suspected pregnancy (see Use in Specific Populations (8.4).

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