DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

James Booker
Director Quality and Regulatory Affairs
WellSpring Pharmaceutical Corporation
9040 Town Center Parkway, Suite 205
Bradenton, FL 34202

RE: NDA # 13-174
Dyrenium® (triamterene) Capsules
MACMIS ID # 14823

Dear Mr. Booker:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional print advertisement (ad) (DYR PPO 0021) for Dyrenium® (triamterene) Capsules (Dyrenium) submitted by WellSpring Pharmaceutical Corporation (WellSpring) under cover of Form FDA 2253. The ad overstates the efficacy of Dyrenium, presents an unsubstantiated superiority claim, and omits important risk information for the drug. Therefore, the material misbrands Dyrenium in violation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 352(n) & 321(n), and FDA implementing regulations, 21 CFR §§ 202.1(e)(5); 202.1(e)(6)(i), (ii), (vii). These violations concern us from a public health perspective because they suggest that Dyrenium is more effective and safer than demonstrated.

Background

The Indications and Usage section of the Dyrenium approved product labeling (PI) states, in pertinent part:

> Dyrenium (triamterene) is indicated in the treatment of edema associated with congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; steroid-induced edema, idiopathic edema and edema due to secondary hyperaldosteronism.
>
> Dyrenium may be used alone or with other diuretics, either for its added diuretic effect or its potassium-sparing potential. It also promotes increased diuresis when patients prove resistant or only partially responsive to thiazides or other diuretics because of secondary hyperaldosteronism.

The PI also provides the following safety information, in pertinent part:

> Boxed WARNING
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> Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium-sparing agents, including Dyrenium. Hyperkalemia is more likely to occur in patients with renal impairment and diabetes (even without evidence of renal impairment), and in the elderly or severely ill. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients receiving Dyrenium, when dosages are changed or with any illness that may influence renal function.
>
> CONTRAINDICATIONS
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> Anuria. Severe or progressive kidney disease or dysfunction, with the possible exception of nephrosis. Severe hepatic disease. Hypersensitivity to the drug or any of its components.
>
> Dyrenium (triamterene) should not be used in patients with pre-existing elevated serum potassium, as is sometimes seen in patients with impaired renal function or azotemia, or in patients who develop hyperkalemia while on the drug. Patients should not be placed on dietary potassium supplements, potassium salts or potassium-containing salt substitutes in conjunction with Dyrenium.
>
> Dyrenium should not be given to patients receiving other potassium-sparing agents, such as spironolactone, amiloride hydrochloride, or other formulations containing triamterene. Two deaths have been reported in patients receiving concomitant spironolactone and Dyrenium or Dyazide…
>
> WARNINGS
>
> There have been isolated reports of hypersensitivity reactions; therefore, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage or other idiosyncratic reactions.
>
> Periodic BUN and serum potassium determinations should be made to check kidney function, especially in patients with suspected or confirmed renal insufficiency….

Furthermore, the ADVERSE REACTIONS section of the PI reports that adverse events such as anaphylaxis, rash, photosensitivity, hypokalemia, azotemia, elevated BUN and creatinine, renal stones, jaundice and/or liver enzyme abnormalities, nausea and vomiting, diarrhea, thrombocytopenia, megaloblastic anemia, weakness, fatigue, dizziness, headache, and dry mouth have occurred in association with use of Dyrenium.

Overstatement of Efficacy

The professional print ad is misleading because it suggests that Dyrenium is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The piece includes the claims:

Consider DYRENIUM whenever you write furosemide and prevent the loss of intracellular potassium.

- Preserves potassium and magnesium levels and enhances diuresis
    - Long-term treatment with loop diuretics may induce magnesium depletion
    - Magnesium deficiency may enhance lipid peroxidation and trigger an accelerated growth response in the vessel wall

(emphasis in original)(footnotes omitted). These claims suggest that Dyrenium, by preserving magnesium levels, will prevent enhanced lipid peroxidation and accelerated growth response in vessel walls caused by magnesium deficiency. These latter suggested processes have no relation to Dyrenium's indicated use for edema. Moreover, although Dyrenium preserves magnesium, FDA is unaware of evidence showing that deficiency of magnesium enhances lipid peroxidation and triggers an accelerated growth response in the vessel wall of humans, or that Dyrenium can prevent these effects. The study described in the reference cited as support for this claim is an *in vivo* study in rats[1] and does not provide evidence that Dyrenium has a favorable effect on lipid peroxidation or growth within vessel walls in humans or any clinical benefit arising from such an effect. FDA is not aware of substantial evidence or substantial clinical experience to support this claim. Therefore, this claim misleadingly overstates the efficacy of Dyrenium.

Unsubstantiated Superiority Claim

This promotional piece is misleading because it claims that Dyrenium "[c]orrects or prevents hypokalemia and maintains serum potassium. . . levels more effectively than does potassium supplementation," when this has not been demonstrated by substantial evidence or substantial clinical experience. The reference cited as support for this claim[2] does not constitute substantial evidence because the subjects did not receive an appropriate dose of potassium chloride. In comparing one drug with another, it is important to choose an appropriate dose and dose regimen for both drugs. That is, for a claim of superior effectiveness the comparative trial should use a full or maximum tolerated dose of the comparator drug product in adequate, well-designed, head-to-head clinical trials. Potassium chloride should be dosed according to the individual needs of the patient. In the study cited as support for the aforementioned claim, however, all patients received one gram of potassium chloride twice a day regardless of their individual needs.

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[1] Shivakumar K, Kumar BP. Magnesium deficiency enhances oxidative stress and collagen synthesis *in vivo* in the aorta of rats. Int J Biochem Cell Biol. 1997;29:1273-1278.

[2] Kohvakka A. Maintenance of potassium balance during long-term diuretic therapy in chronic heart failure patients with thiazide-induced hypokalemia: comparison of potassium supplementation with potassium chloride and potassium-sparing agents, amiloride and triamterene. Int J Clin Pharmacol Ther Toxicol. 1988;26:273-277.

Omission of Important Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. This piece presents the boxed warning for Dyrenium, but fails to present other important risk information for the drug, including the contraindications and warnings identified on page 2 of this letter. By omitting this risk information, the piece misleadingly suggests that Dyrenium is safer than has been demonstrated.

Conclusion and Requested Action

Your promotional piece overstates the efficacy of Dyrenium, presents an unsubstantiated superiority claim, and omits important risk information for the drug. Therefore, the piece misbrands Dyrenium in violation of the Act and FDA implementing regulations. See 21 U.S.C. §§ 352(n) & 321(n); 21 CFR §§ 202.1(e)(5)(i)-(iii); 202.1(e)(6)(i), (ii), (vii).

DDMAC requests that WellSpring immediately cease the dissemination of violative promotional materials for Dyrenium such as those described above. Please submit a written response to this letter on or before January 4, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Dyrenium such as those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 14823 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Dyrenium comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Lynn Panholzer, PharmD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lynn Panholzer

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