

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 18-200/S-024

NDA 18-201/S-037

Approval Letter



NDA 18-200/S-024
NDA 18-201/S-037

Merck & Co., Inc.
Attention: Mr. Kenneth A. Kramer
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Mr. Kramer:

Please refer to your supplemental new drug applications dated June 28, 2001 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Midamor (amiloride hydrochloride) 5 mg Tablets and Moduretic (amiloride hydrochloride and hydrochlorothiazide) 5/50 mg Tablets.

We acknowledge receipt of your submission dated February 5, 2002 that constituted a complete response to our August 7, 2001 action letter.

These supplemental new drug applications provide for final printed labeling revised as follows:

NDA 18-200/S-024 (Midamor)

Added **PRECAUTIONS**/Geriatric Use sub-section:

Geriatric Use

Clinical studies of Midamor did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CONTRAINDICATIONS, Impaired Renal Function.)

NDA 18-201/S-037 (Moduretic)

Added **PRECAUTIONS**/Geriatric Use sub-section:

Geriatric Use

Clinical studies of Moduretic did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the

dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CONTRAINDICATIONS, Impaired Renal Function.)

We also noted minor editorial changes.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the final printed labeling included in your February 5, 2002 submission. Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,

{ See appended  electronic signature page }

Douglas C. Throckmorton, M.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doug Throckmorton
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Merck & Co., Inc.
Attention: Mr. Kenneth A. Kramer
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Mr. Kramer:

Please refer to your supplemental new drug applications dated June 28, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Midamor (amiloride hydrochloride) 5 mg Tablets (NDA 18-200) and Moduretic (amiloride hydrochloride and hydrochlorothiazide) 5/50mg Tablets (NDA 18-201).

These supplements provide for draft labeling with the following revision to the PRECAUTIONS/Geriatric Use section of the labeling:

NDA 18-200 (Midamor)

Added sub-section:

Geriatric Use

Clinical studies of Midamor did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CONTRAINDICATIONS, Impaired Renal Function.)

In addition, minor editorial changes were noted.

NDA 18-201 (Moduretic)

Added sub-section:

Geriatric Use

Clinical studies of Moduretic did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CONTRAINDICATIONS, Impaired Renal Function.)

In addition, minor editorial changes were noted.

We have completed the review of these applications and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for these drugs. The labeling should be identical in content to the submitted drafts.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically (to each application) according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL (to each application), ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,



{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Raymond Lipicky
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