

ANDA 75-369 (10 mg and 20 mg)  
75-370 (2.5 mg and 5 mg)

March 28, 2000

Danbury Pharmacal, Inc.  
U.S. Agent for KRKA, d.d., Novo mesto  
Attention: Ann Mullarkey  
131 West Street  
Danbury, CT 06810

Dear Madam:

This is in reference to your abbreviated new drug applications dated April 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Enalapril Maleate Tablets USP.

Reference is also made to the Tentative Approval letter issued by this office on January 29, 1999, and to your amendments to each application dated December 10, 1999 and March 2, 2000.

We have completed the review of these abbreviated applications and have concluded that, based upon the information you have presented to date, the drug products remain safe and effective for use as recommended in the submitted labeling. Therefore, the applications remain **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your applications and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug products), and is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your applications, Vasotec Tablets of Merck Research Laboratories, is currently subject to a period of patent protection (U.S. Patent No. 4,374,829, the "829 patent"). Your applications contain a Paragraph III Certification to the '829 patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market these drug products prior to the expiration of this patent. As noted in the current edition of the Agency's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", the "Orange Book", this patent was scheduled to expire on February 22, 2000. However, Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the

Modernization Act) created Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). Section 505A permits the sponsor of the RLD to obtain an additional six months of patent protection if, in accord with the

statute, the sponsor submits data previously requested by the Agency relating to the use of the drug in the pediatric population. The RLD holder has submitted data to support the use of enalapril maleate in a pediatric population. The Agency's Pediatric Exclusivity Board has determined that the data support the granting of 6-months of exclusivity to the RLD. Consequently, the awarding of this exclusivity will effectively lengthen the life of the '829 patent for an additional 6 months. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the additional exclusivity period granted to the RLD holder has expired; i.e., currently August 22, 2000.

Because the Agency is granting a tentative approval for these applications, please amend each application at least 60 days (but not more than 90 days) prior to the date you believe your applications will be eligible for final approval. These amendments should identify changes, if any, in the conditions under which the products were tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. Because these amendments serve to reactivate your applications, they should be submitted even if none of these changes were made. These submissions should be designated clearly in your cover letters as a MINOR AMENDMENT. In addition to these amendments, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your applications, or may result in a delay in the issuance of the final approval letter(s).

Any significant changes in the conditions outlined in these abbreviated applications as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be

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made.

Please note that these drug products may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of these drug products before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letters, these drug products will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug

Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to August 22, 2000, you should amend your applications accordingly.

At the time you submit any amendments, you should contact Bonnie McNeal, Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

Gary Buehler  
Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and

Research

TENTATIVE APPROVAL (SECOND)