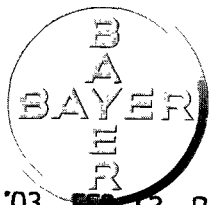
Bayer HealthCare



0588 '03 FEB 13 P3:25

Allen H. Heller, M.D.
Head of Global
Research & Development

February 11, 2003

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Docket: 77N-0094
FDA Rulemaking on Professional Labeling for Aspirin

Bayer HealthCare LLC
36 Columbia Road
P O. Box 1910
Morristown, NJ 07962-1910
Phone 973 408-8015
Fax· 973 254-4856
allen.heller b@bayer.com

CITIZEN PETITION

The undersigned submits this petition under 21 CFR 330.10 to request the Commissioner of Food and Drugs to amend the Final Rule for Professional Labeling for Aspirin to include the use of 75mg-325mg aspirin for the primary prevention of myocardial infarction in those individuals at sufficient risk.

This request is supported by the submission of five landmark primary prevention trials:

- Physician's Health Study (1988)
- British Doctors' Trial (1988)
- Thrombosis Prevention Trial (1998)
- Hypertensive Optimal Treatment Study (1998)
- Primary Prevention Project (2001)

The Citizen's Petition summarizes the results of five major clinical trials in primary prevention, involving over 55,000 subjects. These trials demonstrate in the aggregate that aspirin significantly reduces the risk of a first non-fatal MI by 32%. Based on an independent review of these trials, the American Heart Association (AHA) and the U.S. Preventive Services Task Force (USPSTF) published guidelines within the last year recommending that patients with sufficient risk of a first MI be considered for aspirin therapy. The proposed labeling revision is based on the AHA guidelines. The AHA recommends that individuals with a 10-year risk equal to or greater than 10% be evaluated for treatment with aspirin as the benefits outweigh the risks.

77N-0094 CP 16

Bayer looks forward to working closely with the Agency to facilitate the prompt approval of this new indication for aspirin. We believe that your approval of this indication will help to improve the health and welfare of millions of Americans.

Please contact me at 973-408-8015 or Judy Doyle at 973-408-8181 with questions regarding this submission.

Bayer Healthcare
Consumer Care Division

Allen H. Heller, M.D.
Head of Global Research and Development

Charles H. Hennekens, MD, Dr. PH
Visiting Professor of Medicine &
Epidemiology and Public Health
University of Miami School of Medicine
Director of Cardiovascular Research

Mount Sinai MEDICAL CENTER & Miami Heart Institute

Mailing Address
2800 S. Ocean Blvd , PH-A
Boca Raton, FL 33432 USA

Phone & Fax. (561) 393-8845
E-Mail PROFCHHMD@prodigy.net

February 11, 2003

Douglas Throckmorton, MD
Chief, Division of Cardiorenal Drugs
Food and Drug Administration
1451 Rockville Pike
Document Control Room, HFD110
Rockville, MD 20852

Dear Dr. Throckmorton

About 10 years ago I collaborated with Bayer on their submission of two Citizen's Petitions for the professional labeling of aspirin, which led to actions by the US Food and Drug Administration (FDA). The first concerned a new indication for acute myocardial infarction (MI) and the second was an expansion of the indications for secondary prevention of cardiovascular events.

At this time I have again collaborated with Bayer and, in particular, at the invitation of Allen H. Heller, MD, I have contributed to the efficacy section of their Citizen's Petition for the professional labeling of aspirin to prevent a first MI.

I believe the case has become sufficiently strong for FDA action. You may recall that in 1988 my Physician's Health Study (PHS) of 22,071 had the aspirin component terminated early based on the unanimous recommendation of the external Data and Safety Monitoring Board (DSMB). Their recommendation was due principally to the emergence of a statistically extreme (p less than 1 in 100,000) 44% reduction in a first MI among those assigned at random to aspirin. Our preliminary report was published in NEJM and, working with Richard Peto in Oxford, we coordinated the publication in the BMJ of the British Doctor's Trial (BDT) of 5039, which showed no significant benefit of aspirin on first MI. I had been the first project director of that trial and coauthored this paper but, more importantly, both Richard and I considered the BDT a pilot for the PHS. Unfortunately, these simultaneous publications led to substantial confusion since the two trials were misinterpreted as showing divergent and inconsistent results. To overcome this confusion, Richard and I, along with George Hutchison, Chair of the PHS DSMB and Richard Doll, published in NEJM a meta-analysis of the two trials. Considering the effect of aspirin on first nonfatal MI, the PHS showed a 42%(+/-9SE) reduction (p less than 1 in 100,000) and the BDT showed a 3%(+/-19SE) non-significant reduction. Due to the far larger sample size of the PHS an overview or meta-analysis demonstrated a 33%(+/-9SE) reduction (p less than 2 in 100,000). In 1989, following publication of the

final report of the PHS in NEJM and an extensive FDA on-site audit which occurred over several weeks, my colleagues and I presented to the Cardiorenal Drug Advisory Committee (CRDAC) of FDA on behalf of Bristol-Myers Squibb, who had supplied the aspirin and placebo as well as packaging for the NIH funded PHS.

All six members of CRDAC who participated in the deliberations voted to professionally label aspirin to prevent a first MI, and the two who had only read the preliminary materials and voted in absentia voted against, so the final vote was 6-2. The FDA did not accept the recommendation of the CRDAC. Since that time, three additional large-scale primary prevention trials, Thrombosis Prevention Trial (TPT), Hypertension Optimal Treatment Study (HOT), and Primary Prevention Project (PPP) have been published, and all show significant benefits of aspirin. Subsequent to the publication of TPT and HOT, but before publication of the PPP, I had published a meta-analysis demonstrating significant benefits of aspirin of about 32% (p less than 1 in 100,000) on first MI and 13% (p less than 1 in 100) on all important vascular events. After publication of PPP, the US Preventive Services Task Force as well as American Heart Association have recommended aspirin prophylaxis for all men and women whose 10 year risks of a first cardiovascular event are 6% or greater and 10% or greater, respectively. Since the publication of PPP, my colleagues and I have an update on aspirin in the primary prevention of cardiovascular diseases, which is in press in the Archives of Internal Medicine.

Following several informal and productive discussions with Ray Lipicky, you, Bob Temple, and Charlie Ganley over the last year, it is my impression that you have secured both the PHS audit as well as the HOT database to guide you in your final decision. I would like to emphasize that Bayer has chosen to use my updated meta-analysis as the basis for their efficacy section as well as to support the more conservative AHA position to further enhance the positive benefit to risk ratio.

In conclusion, I believe that prompt action by FDA is both important and timely and has the potential for a substantial positive clinical and public health impact.

Please do not hesitate to contact me if you require further information.

With kindest personal regards.

Yours sincerely,

Charles H. Hennekens /bh

Charles H. Hennekens

cc Allen H. Heller, MD

Table of Contents

Guide to Tables