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David W. Feigal, Jr., MD, MPH  
Director, Division of Antiviral Drug Products  
Office of Drug Evaluation II  
U.S. Food and Drug Administration  
Rockville, Maryland 20857

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OFFICE MANAGEMENT BRANCH

Re: Over-the-counter acyclovir  
Docket #94N0006

Dear Dr. Feigal:

I served as the chair of the STD Subcommittee of the anti-infective treatment guidelines project undertaken by the Infectious Diseases Society of America under a contract from FDA. I write to express my views on OTC acyclovir; I agree with the perspectives of the IDSA to be presented by Dr. Thomas Beam at the May 19 hearing. From a scientific/public health standpoint, I have two major concerns and one minor one. I also have a social/political concern.

1. The first of my major concerns is that OTC acyclovir may encourage the spread of genital herpes. To the extent that all STDs, probably including herpes, have the potential to enhance the efficiency of HIV transmission, my concern goes well beyond the effect on herpes itself. It will be argued by Burroughs Wellcome that widespread use of acyclovir by infected persons will reduce the number of infectious days, thereby reducing the potential for ongoing transmission. Countering this positive effect, however, is the fact that persons on acyclovir will tend to be more sexually active. Although this potential may be reduced by an education/advertising campaign, human nature dictates (and the cumulative experience of STD experts confirms) that persons without genital symptoms and those with trivial symptoms are far more likely to be sexually active than those with severe symptoms. Because most persons with overt genital symptoms modify or entirely cease their sexual activity, the major transmitters of all STDs are in the subset of patients with absent or trivial symptoms. In other words, it is simply not realistic to believe that persons who self-treat themselves with acyclovir will not be more inclined to be sexually active without barrier protection than they would with symptomatic disease. To be honest, I do not know where the balance lies--i.e., whether the biological effect of reduced transmissibility or the behavioral effect of increased sexuality will be dominant. In the absence of definitive knowledge, however, surely it is appropriate to err on the side of caution.
2. My second major concern is the potential for selection of acyclovir-resistant mutants of HSV and perhaps VZV. Although it will be argued that to date this has been a substantial problem only in immunodeficient persons, that fact probably is related to the frequency of acyclovir usage in those populations. That experience might well be duplicated if acy-

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clovir is available OTC because of intermittent and prolonged therapy, often at suboptimal dosage, by large numbers of infected persons. Although thymidine kinase-negative HSV strains seem to lose some virulence, this does not appear to be the case for other forms of acyclovir resistance. It flies against all that we know about anti-infective drugs and microbial genetics to believe that there is no potential for selection of resistant strains of HSV. As in my first point, the prudent course is to err on the side of caution; i.e., in the absence of proof that significant resistance will not result, we should not undertake this potentially disastrous national experiment.

3. My third concern is that persons with other STDs, especially those associated with genital ulceration, will treat themselves with acyclovir in the belief they have herpes, delaying diagnosis and enhancing transmission and complications of chancroid, syphilis, or other STDs. Actually, I believe the potential for this problem is relatively small, primarily because chancroid and syphilis remain relatively uncommon. They also are heavily concentrated in socially and economically disadvantaged populations, in whom acyclovir use might be anticipated to be low. Nevertheless, the potential for localized outbreaks and transmission of disease to at least a modest number of new sexual partners should not be discounted.
4. My final concern, as I said above, is more social/political than scientific. At a point in time when infectious disease physicians, microbiologists, and the FDA are coming to recognize the extreme hazards we now face due to relatively unrestricted use of antibiotics, it seems particularly inappropriate to loosen the reins on an entirely new class of anti-infective drugs. Making any antiviral drug available OTC at this point in time is a terrible precedent.

As a socially conscious physician with great empathy for persons with genital herpes, especially those with frequent recurrences, I fully understand their desire for easy access to acyclovir. A minority of genital herpes sufferers would have significantly reduced health care costs and perhaps improved psychological well-being if acyclovir were available OTC. Many such persons (and agencies that speak for them, such as the American Social Health Association) will testify as to the relative reliability of such persons--i.e., that they will use the drug appropriately and will exercise care to prevent infecting other persons. However, such herpes patients are the small tip of a very large iceberg. As much as I understand their concerns, I do not believe that the advantages to them outweigh the potential adverse effects of OTC acyclovir for the population as a whole.

I hope this information is helpful. Please let me know if you have any questions.

Sincerely,



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Professor of Medicine  
University of Washington

Director, STD Control Program  
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