Guidance for Industry

OTC Treatment of Herpes Labialis with Antiviral Agents

Draft — Not for Implementation

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For questions on the content of the draft guidance, contact Joseph Toerner, 301-827-2330

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical Medical

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I. INTRODUCTION

This guidance is intended to assist those interested in developing antiviral agents to treat herpes labialis over the counter (OTC). Because there are outstanding issues related to the potentially inappropriate use of OTC antiviral products and the unknown potential implications for cross-resistance to other members of this class of drugs, the Center for Drug Evaluation and Research (CDER) believes that antiviral drugs for the treatment of herpes labialis should not be sold OTC in the United States at this time. Sponsors who are considering proposing in the future the OTC use of antiviral products for the treatment of herpes labialis should thoroughly evaluate issues relating to misuse and resistance before submitting an application for marketing.

II. DISCUSSION

Because of the interest on the part of individuals, professional groups, and drug manufacturers in marketing antiviral agents for OTC treatment of herpes labialis, CDER has decided to state publicly its current view on this topic.

The clinical spectrum of herpes infections varies widely, ranging from self-limiting disease such as herpes labialis to serious and life-threatening conditions such as neonatal herpes infection and herpes encephalitis. Currently, the antiviral drug products that are effective in the treatment of all of these conditions are members of a single drug class, the acyclic guanosine analogue class.

The emergence of herpesvirus (HSV) isolates that are resistant to each of the marketed acyclic guanosine analogues has been documented. It is generally believed that the development of resistance is more commonly associated with HSV-2 than HSV-1 and that a higher frequency of HSV resistance, overall, occurs among immunocompromised individuals than among those with intact immune systems. Because of a common mechanism of action, it is also generally believed that the rate of cross-resistance between the available acyclic guanosine analogues is nearly complete. Thus, the Agency is concerned that misuse of these drugs could hasten the development of HSV resistance, jeopardizing the usefulness of the entire class of agents for treatment of serious and life-threatening herpes infections. This concern is further enhanced by the fact that currently no other classes of agents are available that have safety and efficacy comparable to the acyclic guanosine analogues in the treatment of these infections. These

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the OTC treatment of herpes labialis with antiviral agents. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

concerns reflect a long-term public health issue with broader implications than safety and tolerability in an individual patient.

The Agency has previously approved the prescription marketing of an antiviral product for treatment of herpes labialis. Patients receive prescription products under the supervision of a licensed healthcare practitioner, and thus the potential for inappropriate use may be more limited in that setting. It is, however, more difficult to predict the degree of inappropriate use that might occur with an OTC antiviral product and the resulting effects.

Discussions at an Antiviral/Nonprescription Drugs Advisory Committees Joint Meeting held on December 1, 1998, indicated that issues related to misuse and resistance should be thoroughly evaluated before weighing the benefits of an OTC antiviral product to treat recurrent herpes labialis against potential public health risks. Products that are proposed for OTC marketing routinely undergo actual use studies to determine how the produces are used by consumers and to assess whether they can be used properly and effectively in an OTC setting. The Agency acknowledges that studies that evaluate not only the potential for misuse but also the potential effects of misuse on the prevalence of drug-resistant herpes strains in our population may be difficult, time-consuming, and resource intensive. However, sponsors who are thinking about proposing the OTC use of antiviral products for the treatment of herpes labialis should address these issues. Issues identified by the Agency and the Advisory Committee members are listed here.

1. How appropriately would a herpes labialis OTC antiviral product be used compared to a prescription product that is used with the oversight of a healthcare provider?

2. What might the consequences be of HSV resistance resulting from the inappropriate use of an OTC antiviral product in the absence of healthcare provider counseling? Potential circumstances of misuse that might increase emergence of resistant HSV include (a) use of an OTC antiviral to treat sexually transmitted diseases including genital herpes, (b) use outside of labeled recommendations for the frequency and duration of dosing, or (c) inappropriate use in immunocompromised individuals.

3. What would the public health effects be of the transmission of drug-resistant HSV?

4. What is the pathogenic potential of drug-resistant HSV?

5. What would the effect be of HSV latency on the ability to evaluate the effects of selective drug pressure on the prevalence of HSV resistance? One concern raised by experts is that prevalence estimates of resistance may actually reflect the susceptibility patterns of virus that were acquired earlier in life. Thus, routine surveillance of HSV resistance in the general population may not reflect the effects of increased drug pressure for many years thus providing false reassurance.

6. How can we be sure that methods for specimen collection, isolation, and susceptibility testing for herpes viruses are reliable, reproducible, and uniformly standardized?