Safety and Efficacy Evaluation of Pleconaril for Treatment of the Common Cold

Str—We read with interest the reports of 2 clinical studies of pleconaril for potential treatment of the common cold [1]. On 19 March 2002, the Antiviral Drugs Advisory Committee of the US Food and Drug Administration (FDA) voted unanimously to recommend that pleconaril not be approved for treatment of the common cold [2]. The committee was concerned about the limited population in which efficacy had been demonstrated, development of resistant viral strains, and reduction in the effectiveness of oral contraceptives.

In these 2 pivotal studies, pleconaril produced modest reductions of 0.5 and 1.0 days in the median time to resolution of colds for all randomized patients and for the subgroup of infected patients, respectively, compared with placebo. However, this represented antiviral activity in an enriched population. The study population consisted primarily of healthy white women with a median age of 36 years who initiated therapy within 24 h after the onset of symptoms. Nearly two-thirds of patients screened for entry were excluded because they had had cold symptoms for >24 h. Data submitted to and reviewed by the FDA have demonstrated that pleconaril is not effective if treatment is initiated >24 h after the onset of symptoms. Therefore, because only patients who had had symptoms for <24 h were included, these 2 studies may overestimate the effect that would be seen in a more heterogeneous population. Among smokers, pleconaril produced no treatment benefit in any patient subset. In addition, pleconaril did not reduce the number of nights in which cold symptoms interfered with sleep, time to return to baseline level of activity, or complications of colds (otitis media or sinusitis).

Pleconaril rapidly induces production of CYP3A4, which likely led to the intermenstrual bleeding and other menstrual abnormalities seen in women taking pleconaril and estrogen-based oral contraceptives (OCs), which are metabolized by this enzyme. The Antiviral Drugs Advisory Committee was concerned that low hormone levels may have contributed to 2 pregnancies in OC/pleconaril users during a 6-week cold-prevention study. Although the 2 pregnancies represented a small percentage of OC/pleconaril recipients, there was concern that these cases signaled OC failure. Approximately 27% of women between 15 and 44 years of age use a pill form of contraception. Thus, the population in which the treatment benefit was best demonstrated (36-year-old women) is that in which use of estrogen-based OCs is most likely and, therefore, that in which the risk of OC failure is greatest.

Picornaviral resistance to pleconaril was identified in 24% of patients in the pivotal studies: 13% of baseline isolates were not susceptible to pleconaril, and, by the end of the 5-day course of treatment, reduced susceptibility emerged in 11% of virus isolates tested. There were no data on the transmissibility of resistant viruses or on the severity and duration of illness in patients to whom a resistant virus was transmitted.

In summary, the committee concluded that the marginal treatment effect was outweighed by the risks of OC failure and possible unintended pregnancies, substantial drug interactions, and potential for transmission of resistant viruses. In addition, there was no evidence that these risks could be adequately managed if pleconaril were approved for use in the general population. Russell Fleischer and Katherine Laessig Division of Antiviral Drug Products, Center for Drug Evaluation and Research, US Food and Drug Administration, Rockville, Maryland

References

Antiretroviral Drug Resistance Testing: Potential Use following Nosocomial Exposure to HIV

The excellent summary of the 2003 recommendations of the International AIDS Society—USA panel on antiretroviral drug testing in adults did not mention the potential utility of resistance testing in guiding postexposure prophylaxis (PEP) following high-risk needlestick injury in health care workers [1].

The Centers for Disease Control and Prevention (Atlanta, GA) has received reports of 57 documented and 138 possible cases of HIV seroconversion associated with occupational exposure to HIV in the