FDA approves first HIV protease inhibitor

WASHINGTON, D.C.—Although its advisory panel had earlier expressed several concerns, on December 7, 1995, the U.S. Food and Drug Administration (FDA, Rockville, MD) approved saquinavir for combination use with other antiviral drugs to treat AIDS patients. Developed by Hoffmann-La Roche (Nutley, NJ) under the trade name Invirase, saquinavir belongs to a family of new antiviral drugs that inhibit a key proteolytic enzyme of human immunodeficiency virus (HIV). The drug was approved under FDA's accelerated mechanism, which allows that surrogate endpoints, rather than definitive proof of a patient improvement, can serve as a measure of a drug's effectiveness. Statements from FDA Commissioner David Kessler and other agency officials indicate that the Roche drug is just the first of several other members of this drug class which the agency is likely to see sometime during 1996.

The FDA Antiviral Drugs Advisory Committee, which met in November, had sent out a decidedly mixed message about saquinavir. It expressed concerns over HIV developing resistance to this drug and others of its class; it called for saquinavir not to be used by itself but only in combination with other HIV inhibitors; and it criticized impending dose and formulation changes that the company says it is implementing.

Nonetheless, both FDA officials and advisory panel members seem convinced by recent clinical trials in North America and Europe that this product appears beneficial to AIDS patients. Saquinavir has been tested both as a single therapeutic agent and in combination with two inhibitors of HIV's reverse transcriptase, zidovudine (AZT), U.K.-based-Glaxo-Wellcome's Retrovir and ddC (Roche's Hivid).

When used alone, saquinavir neither raised $CD4^+$ cell counts nor reduced blood levels of HIV (as determined by viral RNA load measurements), according to FDA officials. However, when the protease inhibitor was combined with either AZT or ddC—and particularly when used in triple combination with both the nucleoside analogs—there was a statistically significant reduction in viral RNA load, and increases, on average, of 80 in $CD4^+$ cell levels among enrolled patients. Both such measures are considered "surrogate markers" of clinical improvement for individuals infected with HIV.

While these trials were under way, Roche scientists began reformulating the drug to boost the daily deliverable dose and make more of it biologically available. The initial version of saquinavir came in hard gelatin capsules, making it impractical to administer high doses. Moreover, much of the orally administered drug becomes protein-bound and is rapidly excreted.

The ongoing reformulation of saquinavir and its better performance in combination with other antiviral drugs complicate the picture for those evaluating its therapeutic safety and efficacy. For example, several members of the advisory panel voiced misgivings about its use in "suboptimal doses." There was also concern that food needs to be eaten (at least a "heavy snack") when the drug is administered so that more of it is absorbed. According to Roche representatives, a pilot clinical trial with the reformulated product indicates that higher doses are well tolerated and, apparently, more effective.

The possibility of HIV resistance to saquinavir and other protease inhibitor drugs also concerned advisory panel members and FDA officials. Although such cross-resistance can be detected in vitro, there is no definitive evidence that it will occur among AIDS patients during treatment. Moreover, high-dose treatments with such drugs may forestall the development of resistance to them by the virus, some experts contend.

Despite saquinavir's problems, FDA's Kessler was upbeat about the approval. "The protease inhibitors are a class of drugs that, as a class, is the most active to date against HIV," he said. "Even this formula of this drug in combination has a real effect. It's a first step, and the real issue is what will be coming available in the next 12 months." **—Jeffrey L. Fox**

Ra-ra for budget-free biotech

WASHINGTON, D.C.—Clinton Administration officials recently made public "Biotechnology for the 21st Century: New Horizons," the latest in an occasional series of glossy, strategic reports outlining the role of the federal government in promoting the commercial success of biotechnology. This report focuses on what officials call the "second wave" of biotechnology research, namely efforts affecting agriculture, the environment, manufacturing, and aquaculture, but excluding health.

Biotechnology in general, and especially underemphasized specialty fields within it, is "poised to make major contributions to the economic growth of the United States and the world in the 21st century," according to the report. "The full potential of biotechnology will only be realized if we continue to invest in a strong national research base and extend our efforts into new application areas," adds presidential science advisor, John Gibbons.

Although the report lays out "overarching priorities" where federal investments could accelerate research progress (. . ."strengthen" this. . ."do" that. . ."facilitate" virtually everything), its message is short on fiscal reality. Thus, with the U.S. federal budget shrinking, not growing, and with several key biotechnology-supporting agencies and departments with programs in these areas in danger of extinction, the likelihood that the report's priorities will be implemented seems to vanish on the near-term horizon. **—JLF**