Teva's MS drug edges to the market

Israel's dominant pharmaceutical company, Teva (Petach Tikva) had waited months for the meeting of the advisory committee of the US Food and Drug Administration (FDA, Rockville, MD) that would decide the future of its multiple sclerosis (MS) drug, Copaxone (Cop-1). But it was worth it. On October 4, Teva was informed by the FDA that Copaxone is approvable as a therapy for the treatment of patients with relapsing-remitting MS. This means the FDA is prepared to grant final marketing approval upon satisfaction of labeling and other postapproval requirements on the part of Teva.

Aharon Schwartz, Teva's vice president of R&D and head of Cop-1 development, says that the company is betting that the drug will energize its small pipeline. "If Copaxone takes a decent market share from the two beta-interferons currently on the market [Berlex Laboratories' (Wayne, NJ) Betaseron (IFN β-1b) and Biogen's (Cambridge, MA) Avonex (IFN β-1a)], investors will have more faith in us. This will allow us to invest more in new R&D, and make use of the science being developed here in Israel." The company has an FDA-inspected plant waiting to manufacture commercial quantities of their drug and already plans to commission a second. Teva hopes to exceed $1 billion in sales for the first time in 1996.

Two of Teva's three other drugs in development, for Alzheimer's and Parkinson's diseases, were developed at Technion (Haifa, Israel). If Cop-1 succeeds, Schwartz expects that it will significantly add to the non-generics revenues of the company.

Cop-1 was developed at the Weizmann Institute (Rehovot, Israel) in the late 1960s. Researchers wanted to synthesize an analog of myelin basic protein (MBP) in order to study it, not to treat MS. However, said Schwartz, during the course of animal studies, it became apparent that Cop-1 suppressed symptoms of MS-like diseases in animals.

The drug is a mixture of chemically co-polymerized amino acids—glutamic acid, alanine, tyrosine, and lysine. The mixture resembles MBP, a major constituent of the myelin sheath that is progressively destroyed in MS. However, it is also immunologically cross-reactive with all four of the antigens that are implicated in the progression of MS.

Teva believes that this somewhat random nature of Cop-1 explains why individuals of widely variant genetic backgrounds appear to adapt to the drug. It may also explain why

Cop-1 reduces by ~30% the MS relapse rate and the progression of disability.

FDA needed an advisory committee meeting for the drug's approval.

Phase III clinical trials have shown that Cop-1 reduces by about 30% the relapse rate in MS and the progression of disability. This efficacy is comparable to that of the beta-interferons but is won, according to Schwartz, without their side effects. Howard Zwibel, medical director of the Baptist Hospital Multiple Sclerosis Center (Miami, FL), who has 15 patients receiving Cop-1 (as well as many others on beta interferons), supports this. He says the drug is "Not better, but as effective as Avonex and Betaseron, with less side effects."

Zwibel estimates that 400 patients in the US are now taking Cop-1, compared with 8000 on Biogen's Avonex, which was approved in May of this year, and 30,000 on Betaseron. Pharmaceutical analysts expect that Cop-1 can capture somewhere between 15–40% of the market in relapsing forms of MS. That will depend, of course, on the detailed recommendations for Cop-1's labeling. Some physicians suggest that Cop-1's mild side-effects make the drug suitable for newly diagnosed patients with relatively mild MS. Others propose that patients who react badly to interferon could switch.

Several other drugs are also close to entering the MS market. After Cop-1 come two other beta-interferons, both from Ares-Serono's (Geneva) wholly owned subsidiary InterPharm (Nesf Tziona, Israel): Rebif (recombinant IFN β-1a) and Frone (IFN β-1b derived from fibroblasts). Both have recently completed phase III trials, and coincidentally, both are, like Cop-1, licensed from the Weizmann Institute. InterPharm has a new $30 million plant ready for the production of Rebif in Israel.

The plethora of competing β-interferons could represent a significant opportunity for Cop-1. Howard Zwibel says that Cop-1 has a different mechanism of action than the β-interferons, so that "Patients with relapsing-remitting MS may well benefit from combination therapy."

Alexion (New Haven, CT) will be watching the progress of Cop-1 with intense interest. Its compound, MP4, is composed of myelin basic protein (which represents around 30% of the myelin sheath) and proteolipid protein (which represents 50% of the myelin sheath). Alexion CEO, Leonard Bell, believes that the more highly defined nature of MP4 could make it a better drug than Cop-1. That, of course, remains to be seen: The clinical testing of the compound will begin in a few months. *Vicki Brower*

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Antiinfectives: Progress marked at ICAAC

Researchers reported preclinical and clinical progress for several antifungal and antiviral biotech drugs during the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, held mid-September in New Orleans, LA. Nexstar Pharmaceuticals (Boulder, CO), announced clinical results for Ambisome, a lipid-encapsulated amphotericin B, showing it has lower toxicity and is more effective than unencapsulated antibiotic. These results were demonstrated in two separate studies, one involving HIV-infected patients in Europe with cryptococcal meningitis and the other cancer patients in Australia with invasive aspergillosis. Data from these clinical trials will now be included in the Nexstar's NDA (new drug application) being filed with the Food and Drug Administration (FDA, Rockville, MD).

Researchers from Merck (Whitehouse Station, NJ) presented results showing that a new class of fungicidal agents called eichonocandins, show potent activity in preclinical studies against several types of pathogenic fungi, including *Candida* and *Aspergillus* species. Eichonocandins are lipopeptides that act by inhibiting cell wall synthesis in fungus. Merck researchers say the eichinocandin designated L-743,872 has been so successful that it is now in phase II clinical trials

Gilead Sciences (Foster City, CA) also reported advances with its antiviral drug designated GS 840. A prodrug, the orally administered nucleotide analog inhibits viral DNA polymerase in its active form. Researchers said the drug had demonstrated effectiveness in reducing viral titer in the blood levels of hepatitis B patients with chronic infections—including some who had been treated unsuccessfully with interferon-alpha. Gilead says the drug also is being tested in a phase II/III study in patients with HIV. *Jeffrey L. Fox*