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AYERST PLANNING ON FIRST QUARTER 1986 NDA SUBMISSION FOR ALREDASE (TOLRESTAT) IN DIABETIC NEUROPATHY; FIRM IS SHOOTING FOR EARLY 1987 MARKET LAUNCH

by The Pink Sheet

Ayerst is targeting the first quarter of 1986 for the filing of its Alredase (tolrestat) NDA for diabetic neuropathy, Ayerst Exec VP-Scientific Affairs John Mullane, MD/PhD, said at American Home Product's June 4 meeting with analysts in New York City. Alredase entered a U.S. multicenter trial for peripheral neuropathy in June 1983, Mullane said. "Over 420 patients will complete efficacy tests at six months and over 250 will complete one year of safety evaluation," Mullane noted, when the firm breaks the code for the triple-blind placebo trial this coming fall. Mullane added that results from Ayerst's nonblinded trials "are very promising." Under Ayerst's current development schedule for Alredase, the firm is projecting an early 1987 market launch. At that time, Ayerst will still have 15 years remaining on the U.S. product patent for tolrestat, Mullane said. During Q&A, Mullane was asked if Ayerst's market launch target date might be unrealistic. In response, he pointed out that Alredase carries FDA's 1-A rating (new chemical entity representing an important therapeutic gain). "FDA has a track record of approving this class of drugs very fast," Mullane said. "Ten months is not an unusual time period for approval." In addition, he noted, that FDA has been reviewing both Ayerst's tolrestat and Pfizer's sorbinil data for safety "on an on and off basis." Because FDA will be familiar with the side effect profile of both drugs, Mullane predicted that FDA's "greatest time effort will be reviewing the efficacy data." Ayerst Seeking Ultradol

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Claim For "Reversal" of Rheumatoid Arthritis; Predicts Filing By 1988 Asked to comment on Ayerst and Pfizer's race to get the first aldose reductase inhibitor on the market, Mullane predicted that the two firms would be "extremely close on filing dates." Mullane said. "I believe [Pfizer] will break the code for their U.S. multicenter study [for sorbinil] in August. We will break our code in late October- early November. Historically, we can put together a large NDA in 3-1/2 months." Discussing the preliminary test results, Mullane said that while Alredase therapy begins to show positive results at eight weeks, "you see maximum results by six months." In Ayerst's open label trials, Mullane noted that "87% of patients with painful neuropathy . . . had reduction of their pain from 'severe to very severe' to 'mild to moderate' levels after six months." Mullane reported that Ayerst's open label studies have had a 4% drop out rate, while "approximately 8%" of patients in the triple-blind U.S. multicenter trials have withdrawn. However, he pointed out that many of the withdrawals were the result of medical complications stemming from the patient's diabetes. "We know of no side effect that we can clearly say is related to tolrestat," he said. Mullane also indicated that tolrestat might have side effect advantages over Pfizer's sorbinil. He asserted that, unlike tolrestat, sorbinil is in "a chemical class with known side effects." In addition to Alredase, Mullane highlighted two other major compounds in development, Ultradol (etodolac) and Ceractin (vinpocetine). Ayerst expects both to make big contributions to sales. Ultradol has been under review at FDA since December 1982 as an analgesic, and since October 1983 for arthritis. Ayerst President Judson St. John predicted at the analsts meeting that Ultradol would be approved by FDA for both analgesic and arthritis claims "in early 1986." However, Ayerst is also seeking what it calls a "breakthrough claim" for Ultradol for the reversal of rheumatoid arthritis. Following rat studies that showed reversal of joint damage with Ultradol, Ayerst initiated a large U.S. clinical study comparing 300 mg Ultradol with 4,100 mg aspirin. Based on the results of that study, Mullane declared "etodolac compared to aspirin retards the progression of rheumatoid arthritis at a relatively low dose of 300 mg a day." Ayerst submitted the results of this study to FDA in November 1984. Noting that the company believes that a higher dose of Ultradol "may reverse the disease process" of rheumatoid arthritis, Mullane noted that Ayerst is currently conducting disease reversal trials comparing 300 mg to

1000 mg of etodolac per day. The third leg of that trial, Mullane said, is a comparison with 2,400 mg of ibuprofen. He predicted that Ayerst will be ready to file for a reversal of joint damage claim by 1988. Asked if Ayerst's current Ultradol data in rheumatoid arthritis is adequate to support a claim in the U.S. for arresting the disease, Mullane noted that the company had hand K-rays taken of those patients in its aspirin v. etodolac comparative trial for at least six months. "We just analyzed the data last October and we've had very excellent results," Mullane said. "The results are so strong that we can divide the study in half and file two statistically positive trials." However, Mullane cautioned: "It would be presumptuous of me to say that we can get a claim in the U.S. based on this data. I think in many world markets this data will be acceptable for a claim." AHP Has At Least Ten Rx Compounds Pending Approval At FDA With Six More On The Way In 1986 Ceractin, licensed from Gideon Richter, is now in Phase III trials for reversal of senility and is expected by Ayerst to reach the NDA stage by late 1986, Mullane indicated. "Basically, patients are given various psychometric testing to see if their varying performance skills will improve on the drug," Mullane noted. "We have completed . . . four single-center placebo controlled trials and those have been positive studies. We have two major U.S. multicenter studies ongoing -- - the first will finish in November, the second in mid-year [1986] -- - and these will be the basis of our NDA." Mullane also commented on six other Ayerst compounds in development, including: Betacor (cetamolol), which is scheduled to reach FDA review for hypertension by May 1986 and for glaucoma by the end of 1986; the antihyperlipidemic acifran, which is expected to reach the NDA stage "near year end 1986"; the dopamine agonist ciladopa, which is targeted for a 1987 NDA filing; the cardiotonic pelrinone, now in Phase IIs; the vasodilator AY 28228, in early clinicals; and the long acting analgesic, AY 30068, which is expected to enter Phase I trials during the first quarter of 1986. Overall, AHP execs commented on over two dozen new chemical entities in varying stages of development. AHP now has at least ten new products, not including line extensions, awaiting FDA approval and is on track to file another six NDAs by the end of 1986, including four Ayerst agents (Alredase, Ceractin, Betacor, and acifran), one Ives drug (Meptid I.V.), and a Wyeth drug (thiazinamium chloride). Wyeth's drug development program includes four agents pending approval at FDA including three

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