**Bis-Pom PMEA--**

Bis-Pom PMEA, also known as adefovir dipivoxil, is an inhibitor of reverse transcriptase but belongs to a new class of antivirals called nucleotides, which appear to have a different mechanism of action than nucleosides. Bis Pom PMEA is taken in a tablet once a day with or without food, but must be taken with oral L-carnitine 500 mg once per day because the compound (PMEA) is associated at high doses with a decrease in serum (blood) carnitine levels. L-Carnitine is a food supplement available over-the-counter. PMEA is a broad spectrum antiviral which means it may have application against other viruses such as herpes, CMV and hepatitis B. Preliminary clinical results and in vitro studies suggest that the development of resistance may not be as great a concern as it has been with protease inhibitors, NNRTIs and nucleosides.

Another feature of PMEA is that the drug does not exit quickly from the cell it enters; a reservoir of drug is established within the cell. This may be responsible for its long half-life and the once-a-day dosing.

A phase II trial enrolled 72 individuals randomized to 125 mg once per day (n=24), 250 mg (n=24) once per day or to placebo (m=24); participants were not taking any other anti-HIV drugs, had CD4 >200 and viral load >10,000 copies/ml. After an initial phase of 12 weeks, the median reduction in HIV-RNA (viral load) was 0.5 log (n=20) from baseline for the 125 mg once per day dose; in fact, the 250 mg dose RNA reduction was slightly less; subsequent studies are using a dose of 120 mg once per day; the average increase in CD4 counts after week 12 was 57 cells. Five individuals had high-level resistance to AZT prior to receiving study drug and did have a decrease in viral load after the 12 weeks of Bis-Pom PMEA monotherapy, though not as great as those individuals without high-level resistance.

After the initial phase of the study, the maintenance phase began in which individuals received Bis-Pom PMEA 125 mg once per day, but were permitted to add nucleosides. Data so far analyzed for 30 participants completing 6 months of maintenance phase therapy indicate a median 0.6 log reduction in HIV-RNA. Gilead Sciences, the developer of Bis-Pom PMEA, say that preliminary data suggest that resistance does not emerge readily from prolonged therapy so far after 6 months of therapy or longer. Gilead reports that, during the maintenance phase, those who were not responsive due to significant AZT-resistance appeared more responsive after additional therapy was permitted. It remains uncertain how responsive a person will be to PMEA, if they have significant AZT-resistance.

Several large trials have started or are about to begin for the purpose of accumulating data for approval. A number of smaller studies are planned to explore the use of PMEA in a variety of multi-drug combinations for individuals at several stages of HIV disease progression (early, intermediate and advanced HIV). As well, ACTG 359 is planning to study PMEA in combination with ritonavir+saquinavir+delavirdine in individuals for

whom indinavir is failing. Preliminary results from the initial study of its application to hepatitis B are encouraging; additional studies for hepatitis B are ongoing and planned.

Although not as potent as a protease inhibitor or a NNRTI, adefovir could play an important role in combination therapy because it will present a new treatment option for those who've exhausted nucleoside or other therapies; with the possible exception of those with extensive AZT resistance, based on the limited data available prior nucleoside experience does not yet appear to limit its effectiveness. It may prove to be even more valuable, if it is established that resistance to PMEA does not easily develop. Observed side effects so far include mild to moderate gastrointestinal complaints (diarrhea, nausea), fatigue, elevated creatinine, protein in urine, and elevated liver enzymes (n=8/219, usually grade 3 which is 5-10 times upper limit of normal). It is preliminary to draw conclusions about the future efficacy and safety of Bis-Pom PMEA until further data is compiled and analyzed.