

HCV ADVOCATE WEEKLY NEWS REVIEW

Review of HCV, HBV and HIV/HCV Coinfection Related News and Highlights

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October 4th, 2004

Bristol-Myers Squibb Submits Applications in U.S. and Europe to Market Entecavir, an Investigational Antiviral Treatment for Chronic Hepatitis B Infection

Source: PRNewswire

PRINCETON, N.J.,-- Bristol-Myers Squibb Company (NYSE: BMY - News) today announced the submission of a New Drug Application to the U.S. Food and Drug Administration for entecavir, an investigational antiviral agent under development for the treatment of chronic Hepatitis B. In the European Union, the Company also submitted a marketing authorization application for entecavir to the European Medicines Evaluation Agency.

Entecavir is an investigational oral antiviral discovered at Bristol-Myers Squibb that is designed to selectively inhibit the Hepatitis B virus, blocking all three steps in the replication process.

Bristol-Myers Squibb is a global pharmaceutical and related health care products company whose mission is to extend and enhance human life.

Source: Bristol-Myers Squibb Company

October 5th, 2004

Valeant Pharmaceuticals to Present Remofovir Pharmacokinetic and Pharmacodynamic Data from Phase 1 Clinical Trial

Source: *PRNewswire*

COSTA MESA, Calif., -- Valeant Pharmaceuticals (NYSE:VRX) announced that an abstract based on remofovir pharmacokinetic (PK) and pharmacodynamic (PD) study data has been posted to the American Association for the Study of the Liver Conference (AASLD) Web site. Valeant submitted the abstract based on data from a Phase 1 clinical trial of remofovir, which is being developed in oral form for the treatment of chronic hepatitis B (HBV), for presentation at AASLD. Valeant will present the data at AASLD in Boston on November 2, 2004.

The remofovir double-blind, placebo-controlled, parallel group, multiple-dose Phase 1 study consists of 45 adult Asian patients with compensated HBV infection. All patients were 18 years or older and had an HBV DNA viral load greater than or equal to 3,000,000 copies/mL at screening. Eight to ten patients were randomized to each of the remofovir dose groups (5, 10, 20 and 30 mg) or placebo and were dosed for 28 days. Safety assessment included adverse events, physical examination, vital signs and safety laboratory tests. Serum HBV DNA levels were also determined in all patients predosing, and on days one, eight, 15, 21 and 28 of treatment. Following discontinuation of therapy, HBV levels were determined at weeks four, eight and 12 using the COBAS Amplicor assay.

The most frequently reported adverse event among all study patients was upper respiratory infection (30 percent). No dose-related trends regarding safety were identified and no events resulted in a patient being withdrawn prematurely from treatment.

At all doses, serum HBV DNA levels decreased with time. After 28 days of remofovir treatment, the median log(10) HBV decline from baseline was 1.64 at the 5 mg dose, 2.48 at the 10 mg dose, 2.72 at the 20 mg dose and 2.66 at the 30 mg dose. In contrast, the placebo dose group had a median log(10) drop of HBV DNA of 0.03.

A Phase 2 trial of remofovir was initiated in July 2004. The Phase 2 study is an open-label, randomized, multiple dose study that will enroll 220 patients at approximately 20 sites in the U.S., Taiwan, Singapore and Korea. The study consists of five treatment groups: remofovir -- 5, 10, 20 and 30 mg/day, and adefovir dipivoxil -- 10 mg/day. Treatment duration will be 48 weeks, with an interim analysis planned for 24 weeks to evaluate safety and efficacy. Enrollment is ongoing. Phase 2 is one phase in a multi-phase clinical evaluation that may lead to the filing of a New Drug Application

About Valeant

Valeant Pharmaceuticals International (NYSE:VRX) is a global, publicly traded, research-based specialty pharmaceutical company that discovers, develops, manufactures and markets a broad range of pharmaceutical products. More information about Valeant can be found at www.valeant.com.

FORWARD-LOOKING STATEMENTS

This press release contains forward-looking statements within the meaning of the federal securities laws relating to expectations, plans or prospects for Valeant Pharmaceuticals, including funding and conducting clinical trials and expected research and development expenses. These statements are based upon the current expectations and beliefs of Valeant Pharmaceuticals' management and are subject to certain risks and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. These risks and uncertainties include market conditions and other factors beyond Valeant Pharmaceuticals' control, the company's success in identifying and enrolling patients in the clinical trials program, the absence of adverse events that would require the clinical trials to be prematurely terminated, clinical results that indicate continuing clinical and commercial pursuit of Viramidine is advisable, and the risk factors and other cautionary statements discussed in Valeant Pharmaceuticals' filings with the U.S. Securities and Exchange Commission.

For more information, please contact Jeff Misakian of Valeant Pharmaceuticals, +1-714-545-0100, ext. 3309.

Source: Valeant Pharmaceuticals International

CONTACT: Jeff Misakian of Valeant Pharmaceuticals, +1-714-545-0100, ext. 3309

October 6th, 2004

Money Unfairly Spent: Hep C Victims

Source: www.cbc.ca

TORONTO - Advocates for hepatitis C victims say they will ask the federal auditor general to investigate whether provinces are unfairly diverting money promised years ago.

In 1998, then federal health minister Allan Rock announced \$300 million for people who got hepatitis C from bad blood prior to 1986 and after 1990. It was to be distributed among the provinces to cover health-care costs not covered by medicare.

However, in the case of Ontario, the money promised to victims is sitting in the province's general revenue fund.

FROM MAY 22, 2001: Hep C victims say money being misdirected

Ontario Health Minister George Smitherman says the money received from Ottawa to defray medical expenses from the blood-borne disease was never intended to go directly to victims.

He says the previous Conservative government signed a legal agreement with Ottawa to use the money to pay for care for all people with hepatitis C, not just those who contracted it from contaminated blood.

"My understanding is Ontario has been applying these funds in exactly the same manner as every other province in the land. And that is in keeping with the legal agreement that was signed," said Smitherman.

Health ministers from Alberta and Nova Scotia say they've been using the money the same way as Ontario.

“The money went into helping all patients with hepatitis C, as I indicated, we’re helping them with the issue of education, prevention and treatment,” said N.S. Health Minister Angus McIsaac.

John Plater, the president of Hemophilia Ontario, says the money was supposed to go to people infected by tainted blood. He plans to ask the federal auditor general to investigate.

“The federal government shouldn’t be allowed to stand up in public and tell the world how they’re going to spend their money, and then behind close doors, do deals that doesn’t send the money where they said it would go,” said Plater.

Plater says hundreds of people infected by tainted blood have died without the enhanced care and treatment they were promised.

Written by CBC News Online staff

FDA Grants Priority Review to Market Leader Pegasys(R) with Copegus(R) for Treatment of Hepatitis C in HIV Patients

Source: PRNewswire

-- Signals Major Step Toward Satisfying Unmet Medical Need --

NUTLEY, N.J., -- The U.S. Food and Drug Administration (FDA) has granted a six-month Priority Review Status to the supplemental new biologics license application (sBLA) for Roche’s combination therapy of Pegasys® (peginterferon alfa-2a) in combination with Copegus® (ribavirin, USP) for the treatment of chronic hepatitis C in patients co-infected with HIV. Roche submitted this file with the FDA in August 2004.

Pegasys, the most prescribed hepatitis C medication in the U.S., is approved for use alone and in combination with Copegus for the treatment of adults with chronic hepatitis C. Priority review designation was granted for the Pegasys and Copegus submission in co-infected patients because the indication would address an unmet medical need.

“There are currently no approved treatments for the approximately 300,000 people in the United States with HIV who are infected with hepatitis C,” said Juan Carlos Lopez-Talavera, M.D., Ph.D., Senior Medical Director, Roche. “Roche invested in the research to pursue an indication for Pegasys combination therapy in co-infected patients because we recognized that the need is urgent. Liver failure resulting from chronic hepatitis C is now one of the leading causes of death in people with HIV.”

HCV and HIV are the two most prevalent blood-borne infections in the United States, and HCV/HIV co-infection is increasingly recognized as a growing public health problem. According to the Centers for Disease Control, hepatitis C has become a major cause of death for people with HIV. Almost four million Americans are believed to have chronic hepatitis C.

The file submitted to the FDA includes results from APRICOT (AIDS Pegasys Ribavirin International Co-infection Trial), the largest study conducted to date evaluating chronic hepatitis C treatment in patients co-infected with HIV and HCV. APRICOT is one of the six Pegasys studies published in The New England Journal of Medicine. The results showed that 40 percent of patients treated with Pegasys and Copegus achieved a sustained virological response (SVR). SVR refers to a patient’s continued undetectable hepatitis C virus levels in the blood 24 weeks after finishing a course of treatment.

About Pegasys

Pegasys, a pegylated alpha interferon, and Copegus were approved by the FDA in December 2002 for use in combination for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis.

Pegasys is dosed at 180mcg as a subcutaneous injection taken once a week. Copegus is available as a 200mg tablet, and is administered orally two times a day as a split dose.

Roche has backed Pegasys with the most extensive clinical research program ever undertaken in hepatitis C, with major studies initiated to advance treatment for hepatitis C patients with unmet needs, including patients co-infected with HIV and HCV, African Americans, patients with cirrhosis, patients with normal ALT levels, and patients who have failed to respond to previous therapy.

About Roche

Hoffmann-La Roche Inc. (Roche), based in Nutley, N.J., is the U.S. prescription drug unit of the Roche Group, a leading research-based health care enterprise that ranks among the world's leaders in pharmaceuticals and diagnostics. Roche discovers, develops, manufactures and markets numerous important prescription drugs that enhance people's health, well-being and quality of life. Among the company's areas of therapeutic interest are: dermatology; genitourinary disease; infectious diseases, including influenza; inflammation, including arthritis and osteoporosis; metabolic diseases, including obesity and diabetes; neurology; oncology; transplantation; vascular diseases; and virology, including HIV/AIDS and hepatitis C.

For more information on the Roche pharmaceuticals business in the United States, visit the company's web site at: <http://www.rocheusa.com>

Facts About Pegasys (Peginterferon alfa-2a) in Combination with Copegus Indication

- Pegasys®, a pegylated alpha interferon, alone or in combination with Copegus® (ribavirin, USP) is indicated for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A).

Dosing and Administration

- Pegasys, a premixed solution, is dosed at 180mcg as a subcutaneous injection once a week. Copegus, available as a 200mg tablet, is administered at 800 to 1200mg taken twice daily as a split dose. The two products are sold separately.

Combination Therapy Clinical Studies

- The two combination therapy pivotal study findings:
- Study 5, published in the March 2, 2004 *Annals of Internal Medicine*, including 1,284 patients receiving medication, showed that patients with certain genotypes (strains) of the hepatitis C virus should be treated with different dosing regimens of Pegasys and Copegus. The treatment regimens and resulting sustained virological response rates for these groups treated with Pegasys and Copegus therapy were:
- Genotype 1: 48 week duration with 1000 - 1200mg Copegus: 51 percent
- Genotype non-1: 24 week duration with 800mg Copegus: 82 percent, Study 4, published in the September 26, 2002 *New England Journal of Medicine*, including 1,121

patients receiving medication, showed that Pegasys and Copegus combination therapy is a more effective treatment for chronic hepatitis C than interferon alfa-2b and ribavirin. The sustained virological response rate in the Pegasys and Copegus treated patients was 53 percent compared to 44 percent in the interferon alfa-2b and ribavirin group. Sustained virological response refers to a patient's continued undetectable serum hepatitis C RNA levels 24 weeks after finishing a course of treatment.

Adverse Events

- Alpha interferons, including Pegasys, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping Pegasys therapy (see Contraindications, Warnings, Precautions and Adverse Events in complete product information).
- Use with Ribavirin. Ribavirin, including Copegus may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease. Ribavirin is genotoxic, mutagenic, and should be considered a potential carcinogen (see Contraindications, Warnings, Precautions and Adverse Events in complete product information).
- Pegasys is contraindicated in patients with hypersensitivity to Pegasys or any of its components, autoimmune hepatitis, and decompensated hepatic disease (Child-Pugh class B and C) before or during treatment with Pegasys. Pegasys is also contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal. Pegasys and Copegus therapy is additionally contraindicated in patients with a hypersensitivity to Copegus or any of its components, women who are pregnant, men whose female partners are pregnant, and patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).
- Copegus therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men must use two forms of effective contraception during treatment and during the six months after treatment has concluded. Routine monthly pregnancy test must be performed during this time. If pregnancy should occur during treatment or during six months post-therapy, the patient must be advised of the significant teratogenic risk of Copegus therapy to the fetus. Physicians and patients are strongly encouraged to report any pregnancies that do occur to Roche by calling 1-800-526-6367.
- The most common adverse events reported for Pegasys and Copegus combination therapy, observed in clinical trials (nE1), were fatigue/asthenia (65%), headache (43%), pyrexia (41%), myalgia (40%), irritability/anxiety/nervousness (33%), insomnia (30%), alopecia (28%), neutropenia (27%), nausea/vomiting (25%), rigors (25%), anorexia (24%), injection site reaction (23%), arthralgia (22%), depression (20%), pruritus (19%) and dermatitis (16%).
- Serious adverse events include neuropsychiatric disorders (suicidal ideation and suicide attempt), serious and severe bacterial infections, bone marrow toxicity (cytopenia and

rarely, aplastic anemia), cardiovascular disorders (hypertension, arrhythmias and myocardial infarction), hypersensitivity (including anaphylaxis), endocrine disorders (including thyroid disorders and diabetes mellitus), autoimmune disorders (including psoriasis and lupus), pulmonary disorders (dyspnea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic/ischemic colitis), pancreatitis, and ophthalmologic disorders (decrease or loss of vision, retinopathy including macular edema and retinal thrombosis/hemorrhages, optic neuritis and papilledema).

- The complete package inserts for Pegasys and Copegus are available at <http://www.pegasys.com> , or by calling 1-877-PEGASYS.

SOURCE: Roche

Web Sites: <http://www.rocheusa.com>; <http://www.pegasys.com>

Lamivudine Delays Clinical Progression of Hepatitis B

Source: www.gastrohep.com

Continuous treatment with lamivudine delays disease progression in patients with hepatitis B and advanced fibrosis or cirrhosis by reducing risk of hepatocellular carcinoma, reports October 7th issue of *The New England Journal of Medicine*.

At present it is unknown just how effective antiviral therapy is in preventing disease progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis.

Professor Yun-Fan Liaw and colleagues selected 651 patients with chronic hepatitis B who had histologically confirmed cirrhosis or advanced fibrosis.

The participants were randomly assigned in a 2:1 ration to receive lamivudine (100mg per day) or placebo for a maximum of 5 years.

The researchers assigned 436 participants to receive lamivudine and 215 to receive placebo.

The researchers were using ‘time to disease progression’ as their endpoint and this was defined by hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease.

The study was monitored by an independent data and safety monitoring board that also performed the interim analyses of the data.

The researchers terminated the study after a median duration of treatment of 32.4 months because they found that there was a significant difference between treatment groups in the number of end points reached.

Hepatocellular carcinoma occurred in 3.9% in the lamivudine group and 7.4% in the placebo group. *New England Journal of Medicine*

The researchers found that end points were reached by 7.8% of patients receiving lamivudine and 17.7% of those receiving placebo.

The researchers also found that the Child-Pugh score increased in 3.4% of patients receiving lamivudine and 8.8% of those receiving placebo.

However, hepatocellular carcinoma occurred in 3.9% of those in the lamivudine group and 7.4% of those in the placebo group.

The team found that overall, 12% of the patients in the lamivudine group and 18% of the patients in the placebo group reported serious adverse events.

Professor Liaw, speaking on behalf of the team concluded, "Continuous treatment with lamivudine delays clinical progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis by significantly reducing the incidence of hepatic decompensation and the risk of hepatocellular carcinoma".

N Engl J Med 2004; 351: 1521-31

October 8th, 2004

Dosanjh Asks Provinces How They Used Money Intended for Hepatitis C Victims

Dennis Bueckert

Source: www.canada.com

Ottawa - Health Minister Ujjal Dosanjh says provinces should tell the public now what they did with \$300 million intended for hepatitis C victims but never received by them.

"Yes, I'm going to ask them (the provinces) for accountability," Dosanjh told the Commons on Thursday. "I have said my preference is, when there are very, very serious questions being asked, about people who are suffering, people who have suffered injury, the answers should come now so their concerns are satisfied. Yes, I'm asking them (the provinces) to be accountable."

An aide to Dosanjh said the minister is making a suggestion, not issuing a directive.

Each of the provinces signed a separate agreement with Ottawa for a share of the \$300 million "care instead of cash" fund. Each province agreed to report in five years, and for most of them that would mean 2007.

The program was intended for victims excluded from cash compensation because their infection with the virus occurred outside the 1986-1990 period for which Ottawa admitted liability.

Former health minister Allan Rock told the Commons at the time the money would be given to the provinces to make certain "anyone who got hepatitis C through the blood system will have access to the needed medical services and drugs for treatment and care without paying out of their own pockets."

Victims say they have not received any help and most provinces have been reluctant to explain where the funds went. Alberta, the exception, has openly said the money went to improved treatment for hepatitis C in general, not for the specified pre-'86, post-'90 victims.

The issue is awkward for Ottawa because hundreds of so-called forgotten victims are facing hardship, and accumulating evidence has undercut the government's argument that there was nothing it could have done to protect the blood system from hepatitis C before 1986.

Also, the fact federal money was apparently used in unintended ways raises questions about the principle of provincial accountability - relevant in light of the recent \$41-billion federal-provincial health deal.

Hepatitis C activist Mike McCarthy said the federal government should admit its original compensation plan was poorly formulated and extend full cash compensation to all victims regardless of when they were infected.

He said there is still \$1 billion in the compensation fund, unclaimed because there were fewer eligible victims than expected

Clean-Needle Bill Passed by Assembly, 43-28

Terrence Dopp

Source: The Express-Times

Trenton-- The state Assembly on Thursday approved a controversial bill giving intravenous drug users legal access to clean needles, a move supporters said would stop the spread of AIDS.

Capping weeks of debate on a contentious initiative, the lower house approved two pieces of legislation, one allow over-the-counter syringe sales and another letting communities institute needle exchange programs. Both bills passed 43- 28.

Lawmakers also earmarked \$10 million for expanded drug rehabilitation programs.

Proponents see the measures as a way to stem the spread of blood-borne diseases such as HIV and Hepatitis C, which they said have ravaged New Jersey's cities.

"New Jersey is sadly behind the curve on this issue," said Assembly Majority Leader Joseph Roberts, D-Camden, sponsor of the exchange proposal. "This is a life and death issue."

During a 7-hour hearing on the bill and throughout discussion on the issue, the opposing sides cited conflicting studies on exchange success rates done in the U.S. and Canada. New Jersey and Delaware are the only states without legalized needle exchanges.

Under the measure approved by the Assembly, registered users could get free needles by turning in used ones at sites selected by communities. Also, people would be able to buy fewer than 10 syringes without a prescription at pharmacies.

Both pieces of legislation still need the approval of the state Senate and governor.

"No shred of evidence exists that needle exchange programs encourage drug use," said Kathy Ellis, spokeswoman for Gov. James E. McGreevey, who called for the legislation after announcing his resignation. "There is evidence that needle exchange programs save lives."

Roseanne Scotti, an activist who worked to pass the bill, said the state has the fifth-highest number of adult AIDS/HIV cases and the third-highest number of pediatric AIDS cases. She said establishing a needle exchange initiative has taken so long in New Jersey because the impacts of drugs are felt primarily in urban areas.

"It has a lot to do with who we are talking about. The people who are getting infected are poor. They're addicted. And they are largely in the minority community," said Scotti, director of the Drug Policy Alliance. "They don't have anybody to advocate for them."

Detractors claim the programs make the state complicit in drug use and are unfair to taxpayers who don't want to see addicts given access to the syringes.

"It's the wrong approach to a very complex problem," said Assemblywoman Alison Littell McHose, R-Sussex/Morris/Hunterdon. "This is nothing more than the state sponsoring an illegal and socially destructive activity."

Assemblyman John Burzichelli, D-Gloucester/Cumberland/Salem, said health concerns overpower concerns over abetting drug use.

"It's a topic that no one really wants to talk about. Intravenous drug use, and any drug use, still is epidemic in this country in some quarters," he said. "We're not condoning drug use. What we're doing is taking a public health step."

Earlier this month, a Superior Court judge invalidated a needle exchange program in Atlantic City. It has also been tried unsuccessfully in New Brunswick.

Two founders of the New Brunswick program, dubbed the Chai Project, were arrested in 1996 and charged with violating the state's ban on distribution of syringes. In 1997, they were each fined \$500 and had their drivers licenses revoked for six months. Terrence Dopp is Trenton correspondent for The Express-Times. He can be reached at 609-292-5154 or by e-mail at tdopp@sjnewsco.com.

October 9th, 2004

Rituxan May Be Associated with HBV Reactivation and Fulminant Hepatitis

Yael Waknine

Source: Medscape

The U.S. Food and Drug Administration (FDA), Biogen Idec, Inc., and Genentech, Inc., have warned healthcare professionals via letter of postmarketing clinical safety reports of hepatitis B virus (HBV) reactivation along with fulminant hepatitis, hepatic failure, and death in some patients with hematologic malignancies taking rituximab (Rituxan) therapy, according to an alert sent yesterday from MedWatch, the FDA's safety information and adverse event reporting program.

Rituximab is indicated in the treatment of patients with relapsed or refractory low-grade or follicular CD20-positive B-cell non-Hodgkin's lymphoma.

According to the letter, the majority of patients affected received rituximab in combination with chemotherapy. Median time to diagnosis was four months after the initial dose of rituximab and approximately one month after the last dose.

The FDA recommends that patients at high risk of HBV infection be screened before initiation of rituximab therapy. Hepatitis B carriers should be closely monitored for clinical and laboratory signs and symptoms of active HBV infection during rituximab therapy and for several months thereafter.

Rituximab and concomitant chemotherapy should be discontinued in patients developing viral hepatitis, and appropriate treatment including antiviral therapy initiated. The FDA notes that insufficient information is available concerning the safety of resuming rituximab therapy in these patients.

Adverse events related to use of rituximab should be reported to Genentech Drug Safety at 1-888-835-2555. Alternatively, this information can be reported to the FDA's MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, online at <http://www.fda.gov/medwatch>, or by mail to 5600 Fishers Lane, Rockville, MD 20852-9787.

Reviewed by Gary D. Vagin, MD