
Nektar Advanced PEGylation

PEGASYS® from Roche Offers
Hepatitis C Patients Improved Efficacy
and Decreased Dosing Frequency

Increasing the Bioavailability and Efficacy of Drug Molecules Using Nektar Advanced PEGylation

Many chronic diseases, such as hepatitis C, are currently managed with frequent therapeutic injections. The ability to effectively control these diseases and, at the same time, minimize the frequency of the required injections can result in better compliance and improved patient quality of life. Nektar Advanced PEGylation is a clinically proven technology that can extend the activity of drug molecules in the body and therefore reduce the frequency of dosing.

PEG is a simple, water-soluble, nontoxic polymer that is nonimmunogenic, is readily cleared from the body, and has been approved for human administration by mouth, injection, and topical application. When attached to a drug, PEGs can extend the length of action in the body from minutes, to hours, to days — depending on the PEG molecule used.

First-generation, low molecular weight PEGylation technologies have been associated with contamination problems, unstable drug linkages, nonselective attachments, and reduced drug activity. To solve these problems, Nektar scientists created Advanced PEGylation, which provides activated, high molecular weight PEGs that can be linked stably and site specifically to drug molecules, allowing improved and prolonged drug performance.

History of Nektar
Advanced PEGylation

Nektar, formerly Inhale Therapeutic Systems, Inc., acquired Shearwater Corporation, the world leader in Advanced PEGylation, in 2001. Nektar Advanced PEGylation has been clinically proven and was used to create the following products, approved in the United States and/or Europe.

- *Roche's PEGASYS®* (peginterferon alfa-2a) for hepatitis C.
 - *Amgen's Neulasta™* (pegfilgrastim) for neutropenia associated with cancer chemotherapy.
 - *Schering-Plough's PEG-INTRON®* (peginterferon alfa-2b) for hepatitis C.
 - *Pharmacia's Somavert®* (pegvisomant) for acromegaly (Europe, filed in the United States).
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Case Study: PEGASYS® from Roche

The Challenge: Interferon alfa, the standard treatment for hepatitis C, has been associated with poor efficacy, primarily due to its short blood circulation half-life of only a few hours. As a result, the typical treatment regimen included three injections per week.

Roche, maker of Roferon® (interferon alfa-2a), sought a way to improve the performance of its therapeutic, but had been unsuccessful using first-generation PEGylation techniques.

Specifically, Roche had used mPEG 5 kilodaltons (kDa) with an active carbonate to produce a urethane-linked PEG. Clinical trials conducted on the conjugate were unsuccessful because the blood circulation half-life for the conjugate was only slightly improved relative to that of the native protein. Development of the product was therefore halted during Phase II clinical trials.

Roche then sought a research and development partner who could help the company overcome these challenges and achieve better results for the interferon alfa-2a molecule.

The Solution: Roche partnered with Nektar, the leader in Advanced PEGylation, to examine various Nektar Advanced PEGylation chemistries and develop an improved form of interferon alfa-2a.

After careful analysis, Nektar's mPEG2-NHS 40 kDa was identified as the optimal reagent for coupling with the Roche interferon alfa-2a, and an mPEG-IFN conjugate with a molecular weight of approximately 60 kDa was created.

Animal studies and modeling indicated that this conjugate would have the desired pharmacokinetics and activity. Most importantly, the studies suggested that the blood concentration of the conjugate would be essentially constant.

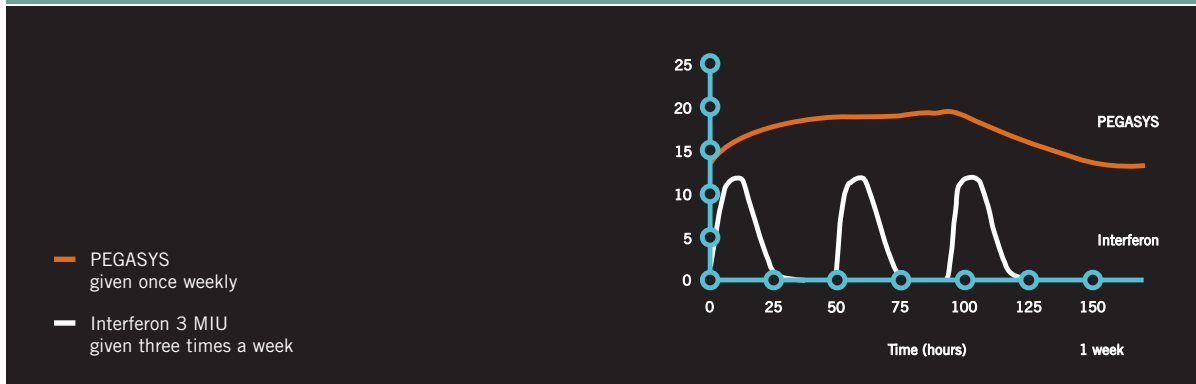
Human clinical trials confirmed the modeling data: essentially constant blood concentrations were achieved with once-a-week subcutaneous injections. Further, Nektar Advanced PEGylation with mPEG2-NHS 40 kDa decreased clearance relative to native IFN and provided an elimination half-life of 77 hours versus nine hours. In addition, the drug exhibited a low volume of distribution and sustained absorption from the subcutaneous injection site.

The Results: The collaboration resulted in the creation of PEGASYS (peginterferon alfa-2a) — a high molecular weight branched PEG molecule linked to interferon alfa-2a — in which the PEG molecule provides a selectively protective barrier against rapid absorption, metabolism, and elimination, while still retaining the drug's ability to attack the virus.

PEGASYS Clinical Results

In a Phase II human clinical trial with 155 patients receiving once-a-week subcutaneous injections of PEGASYS, 62% of patients were free of the virus after 48 weeks of treatment and 36% of patients exhibited a sustained viral clearance 24 weeks later. In comparison, native IFN injected three times per week (standard therapy) gave only a 3% sustained response. A Phase III study with 531 patients supported the Phase II study and showed a sustained response rate of 39%, with a decreased incidence of antibodies formed against the drug from 15% to 1.5%. A second Phase III study with 271 cirrhotic patients showed 43% of the patients receiving PEGASYS had viral clearance at the end of 48 weeks of treatment. Further, PEGASYS reduced the dosing frequency from three times a week for standard therapy to once a week.

Nektar Advanced PEGylation Improves Drug Efficacy



Therapeutic levels following a single dose of PEGASYS have been shown to last more than one full week compared to less than 24 hours with standard IFN therapy. Previously, only about 10% of patients experienced a sustained reduction in viral levels with standard dose IFN therapy, which required dosing three times a week. Results from the Phase III monotherapy clinical trial indicated that PEGASYS raised the reduction of viral levels to 39% and decreased the incidence of antibodies formed against the drug from 15% to 1.5%, while providing the convenience of decreased dosing frequency.

Conclusion: Nektar scientists helped Roche create a breakthrough therapeutic for hepatitis C and a new standard for improving IFN therapy. PEGASYS may offer new hope for the more than 170 million people worldwide who suffer from chronic hepatitis C, a potentially life-threatening condition. Supplied as a ready-to-use solution, PEGASYS is expected to provide longer lasting levels of drug in the blood, which increases efficacy and potentially could reduce long-term liver damage. With the potential for dramatically reduced toxicity and increased efficacy, PEGASYS may greatly improve hepatitis C disease management by reducing side effects as well as the number of injections needed to only one per week.

Nektar offers a comprehensive solution for advanced molecule engineering, including catalog sales of activated PEG derivatives for research use, research collaborations, early clinical development of PEG drugs, CGMP manufacturing of PEG reagents, and industry-leading regulatory support.

Nektar provides a portfolio of leading drug delivery solutions and development expertise to help partners create breakthrough products that fuel their pipelines.

Market Status of PEGASYS

Given the dramatically improved clinical efficacy of PEGASYS over the native IFN, Roche filed for market clearance with the FDA in May 2000. In June 2002, Roche filed a Biologics License Application (BLA) and New Drug Application (NDA) for combination therapy of PEGASYS and COPEGUS™ (ribavirin) tablets for the treatment of chronic hepatitis C in patients without cirrhosis, and with cirrhosis and compensated liver disease. The FDA approved PEGASYS for marketing in October 2002 and approved PEGASYS in combination with ribavirin in December 2002.

Selected References:

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Important Information:

PEGASYS, alone or in combination with COPEGUS, is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alfa. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A).

Alfa interferons, including PEGASYS (peginterferon alfa-2a), 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 a worsening of cardiac disease. Ribavirin is genotoxic and 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 is 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, in women who are pregnant, men whose female partners are pregnant, and patients with hemoglobinopathies (e.g., 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 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. If pregnancy should occur during treatment or during 6 months post-therapy, the patient must be advised of the significant teratogenic risk of COPEGUS therapy to the fetus. To monitor maternal-fetal outcomes of pregnant women exposed to COPEGUS, the COPEGUS Pregnancy Registry has been established. Physicians and patients are strongly encouraged to register by calling 1-800-526-6367.

The most common adverse events reported for PEGASYS and COPEGUS combination therapy observed in clinical trials (N=451) 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 included neuropsychiatric disorders (suicidal ideation and suicide attempt), serious and severe bacterial infections (sepsis), 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).

To learn more about Nektar Advanced PEGylation, part of the Nektar Molecule Engineering solution, or how Nektar can create and optimize a solution for your molecule, contact our Business Development team at [256.533.4201](tel:256.533.4201) or at partnerships@nektar.com. Or visit us on the web at www.nektar.com.



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