Unipeg™ یونیپیگ

(Peginterferon Alfa-2a)

180mcg Solution for Injection

DESCRIPTION

UNIPEG (Peginterferon Alfa-2a) solution for injection is a combination of recombinant alfa-2a with mono-polyethylene glycol, i.e. genetically engineered from *Hansenula Polymorpha,* intended for subcutaneous administration only.

QUALITATIVE AND QUANTITATIVE COMPOSITION

UNIPEG (Peginterferon Alfa-2a) is available as solution for injection to be administered subcutaneously.
UNIPEG (Peginterferon Alfa-2a) 180mcg:
Each vial contains:
Pegylated interferon Alfa-2a...180mcg
per mL of solution for Injection.

CLINICAL PHARMACOLOGY

Mechanism of Action

The conjugation of PEG reagent to Interferon Alfa-2a forms a Pegylated Interferon Alfa 2a. Pegylated Interferon Alfa-2a possesses the *in vitro* antiviral and antiproliferative activities that are characteristic of interferon Alfa-2a.
Interferons bind to specific receptors on the cell surface initiating intracellular signaling via a complex cascade of protein-protein interactions leading to rapid activation of gene transcription. Interferon-stimulated modulate many biological effects including the inhibition of viral replication in infected cells, inhibition of cell proliferation and immunomodulation. The clinical relevance of these *in vitro* activities is not known.
Peginterferon Alfa-2a stimulates the production of effector proteins such as serum neopterin and 2', 5'-oligoadenylate synthesis.

Pharmacokinetics

Peginterferon alfa-2a recombinant shows a pharmacokinetic profile suitable for once weekly administration.
Following a subcutaneous injection of Peginterferon Alfa 2a 180mcg maximum serum levels of Pegylated Interferon Alfa-2a are achieved in 24 hours. The absorption of Peginterferon Alfa-2a is sustained with peak serum concentrations reached 72 to 96 hours after dosing. The absolute bioavailability is 84% and is similar to that seen with interferon Alfa-2a.
Pegylated Interferon Alfa-2a is found predominantly in the bloodstream and extracellular fluid. Pegylated Interferon Alfa-2a is distributed to the liver, kidney and bone marrow in adddition to being highly concentrated in the blood.
The mean terminal half-life after subcutaneous dosing in patients with chronic hepatitis C is 80 hours (range 50 to 140 hours). The terminal half-life determined after subcutaneous administration may not only reflect the elimination phase of the compound, but may also reflect the sustained absorption of Peginterferon.
Dose-propotional increase in AUC and Cmax are seen in patients with chronic hepatits C after once-weekly dosing of Peginterferon.

Site of administration:

Subcutaneous administration of Pegylated Interferon Alfa-2a should be limited to the abdomen and thigh, as the extent of absorption based on AUC was about 20% to 30% higher upon injection in the abdomen and thigh.

Special Populations

Renal Insufficiency: Renal impairment is associated with slightly decreased CL/F and prolonged half-life. In patients with CLcr between 20 and 40 mL/min, the average CL/F is reduced by 25% compared with patients with normal renal function. In patients with end stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in the clearance.

Elderly: In subjects older than 62 years, the absorption of Peginterferon Alfa-2a after a single subcutaneous injection of 180mcg was delayed but still sustained compared to young healthy subjects (tmax of 115 hours vs. 82 hours, older than 62 years vs. younger, respectively). The AUC was slightly increased (1663 vs. 1295 ng□h/mL) but peak concentrations (9.1 vs. 10.3ng/mL) were similar in subjects older than 62 years. A dose of Pegylated Interferon Alfa 2a is not needed in the geriatric patient.

THERAPEUTIC INDICATIONS

Chronic hepatitis B:

UNIPEG (Peginterferon Alfa-2a) is indicated for the treatment of HBeAg-positive or HBeAg-negative-chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis.

Chronic hepatitis C:

UNIPEG (Peginterferon Alfa-2a) is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV.
The optimal way to use UNIPEG (Peginterferon Alfa-2a) in patients with chronic hepatitis C is in combination with ribavirin. The combination of UNIPEG (Peginterferon Alfa-2a) and ribavirin is indicated in naive patients and patients who have failed previous treatment with interferon Alfa (pegylated or non-pegylated) alone or in combination therapy with ribavirin.
Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin.

DOSAGE AND ADMINISTRATION

Treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis B or C.
Chronic hepatitis B:
The recommended dosage and duration of UNIPEG for both HBeAg-positive and HBeAg-negative chronic hepatitis B is 180mcg once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

Chronic hepatitis C:

Peginterferon Alfa 2a Monotherapy

The recommended dose of UNIPEG monotherapy for chronic hepatitis C is 180mcg once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

Peginterferon Alfa 2a & Ribavirin Combination Therapy The recommended dose of UNIPEG when used in combination with ribavirin for chronic hepatitis C is 180mcg once weekly. The daily dose of ribavirin is 800mg to 1200mg administered orally in two divided doses.

Dosing Recommendations for Combination therapy

Genotype	for HCV Patients UNIPEG Dose	Ribavirin Dose	Duration
Genotype 1 LVL with RVR *	180mcg	<75kg=1000mg ≥75kg=1200mg	24 weeks or 48 weeks
Genotype 1 HVL with RVR *	180mcg	<75kg=1000mg ≥75kg=1200mg	48 weeks
Genotype 4 with RVR *	180mcg	<75kg=1000mg ≥75kg=1200mg	24 weeks or 48 weeks
Genotype 1 or 4 without RVR *	180mcg	<75kg=1000mg ≥75kg=1200mg	48 weeks
Genotype 2 or 3 without RVR **	180mcg	<75kg=1000mg ≥75kg=1200mg	24 weeks
Genotype 2 or 3 LVL with RVR **	180mcg	<75kg=1000mg ≥75kg=1200mg	16 weeks or 24 weeks
Genotype 2 or 3 HVL with RVR **	180mcg	<75kg=1000mg ≥75kg=1200mg	24 weeks
Genotype 2 or 3 LVL/HVL with RVR **	180mcg	51-60kg=800mg	16-24 weeks

RVR* = rapid viral response (HCV RNA undetectable at week 4 and HCV RNA undetectable at week 24.

RVR** = rapid viral response (HCV RNA negative) by week 4

LVL (Low viral load) = ≤800,000 IU/mL

HVL (High viral load) = >800,000 IU/mL

The dose should be individualized to the patient depending on baseline disease charactristics (e.g. genotype), reponse to therapy, and tolerability of the regimen.

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype.

Prognostic factors such as degree of fibrosis should be taken into account when deciding on treatment duration.

ADVERSE REACTIONS

Very common: Anorexia, depression, anxiety, insomnia, headache, dizziness, concentration impaired, dyspnoea, cough, diarrhea, nausea, abdominal pain, alopecia, dermatitis, pruritus, dry skin, myalgia, arthralgia, pyrexia, rigors, pain, asthenia, fatigue, injection site reaction, irritability.

Common: Upper respiratory infection, bronchitis, oral candidiasis, herpes simplex, fungal, viral and bacterial infections, thrombocytopenia, anaemia, lymphadenopathy, hypothyroidism, hyperthyroidism, emotional disorders, mood alteration aggression, nervousness, libido decreased, memory impairment, syncope, weakness, migraine, hypoaesthesia, hyperaesthesia, paraesthesia, tremor, taste disturbance, nightmares, somnolence, vision blurred, eye pain, eye inflammation, xerophthalmia, vertigo, earache, tachycardia, palpitations, oedema peripheral, fushing,dyspnoea exertional, epistaxis, nasopharyngitis, sinus congestion, nasal congestion, rhinitis, sore throat, vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, glossitis, stomatitis, flatulence, dry mouth, rash, sweating increased, psoriasis, urticaria, eczema, skin disorder, photosensitivity reaction, night sweats, back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskeletal pain, muscle cramps, Impotence, chest pain, influenza like illness, malaise, lethargy, hot flushes, thirst, weight decreased.

Uncommon: Pneumonia, skin infection, hepatic neoplasm, sarcoidosis, thyroiditis, diabetes, dehydration, suicidal ideation, hallucinations, peripheral neuropathy, retinal hemorrhage, hearing loss, hypertension, wheezing,gastrointestinal bleeding, hepatic dysfunction

Rare: Endocarditis, otitis externa, pancytopenia, anaphylaxis, systemic lupus erythematosus rheumatoid arthritis, diabetic ketoacidosis, suicide, psychotic disorder, coma, convulsions, facial palsy, optic neuropathy, papilloedema, retinal vascular disorder, retinopathy, corneal ulcer, myocardial infarction, congestive heart failure, angina, supraventricular tachycardia, arrhythmia, atrial fibrillation, pericarditis, cardiomyopathy, cerebral haemorrhage, vasculitis, interstitial pneumonitis including fatal outcome, pulmonary embolism, peptic ulcer, pancreatitis, hepatic failure, cholangitis, fatty liver, myositis, renal insufficiency, substance overdose.

Very rare: Aplastic anemia,idiopathic or thrombotic thrombocytopenic purpura, vision loss, toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme.

CONTRAINDICATIONS

- Hypersensitivity to the active substance, to alfa interferons, or to any of the excipients.
- Autoimmune hepatitis.
- Severe hepatic dysfunction or decompensated cirrohsis of the liver.
- Neonates and young children up to 3 years old, because of the excipient benzyl alcohol.
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months.
- Combination therapy containing interferon-Alfa-2a and ribavirin must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of patients taking combination therapy.
-There are no adequate and well controlled studies of Peginterferon

Alfa-2a in pregnant women, therefore, UNIPEG (Peginterferon alfa-2a) should not be used in pregnant women with or withourt in combination with Ribavirin.

WARNINGS

General

Life-threatening or fatal neuropsychiatric reactions may manifest in patients receiving therapy with Peginterferon alfa 2a and include suicide, suicidal ideation, homicidal ideation, depression, relapse of drug addiction, and drug overdose. These reactions may occur in patients with and without previous psychiatric illness. Neuropsychiatric adverse events observed with alfa interferon treatment include aggressive behavior, psychoses, hallucinations, bipolar disorders, and mania. Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. Patients should be advised to report any sign or symptom of depression or suicidal ideation to their prescribing physicians. In severe cases, therapy should be stopped immediately and psychiatric intervention instituted.

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of high or persistent fever must be ruled out, particularly in patients with neutropenia. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

PRECAUTIONS :

General:

Peginterferon Alfa-2a should be administered under the supervision of a qualified physician experienced in the managemnet of hepatitis C. Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (e.g, spherocytosis, history of GI bleeding).

Laboratory tests:

Before beginning Peginterferon Alfa-2a/ribavirin combination therapy,standard hematological and biochemical laboratory tests are recommended for all patients. After initiation of therapy, hematological tests should be performed at 2 weeks and 4
weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy. The entrance criteria used for the clinical studies of Peginterferon Alfa-2a alone or in combination with ribavirin may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count $\geq$90,000 cells/mm^3
- Absolute neutrophil count (ANC) $\geq$1500 cells/mm^3
- TSH and T4 within normal limits or adequately controlled thyroid function.

Endocrine system:

Thyroid function abnormalities or worsening of pre-existing thyroid disorders have been reported with the use of Alfa interferons, including Peginterferon Alfa-2a. Prior to initiation of Peginterferon Alfa-2a therapy, TSH and T4 levels should be evaluated. Peginterferon Alfa-2a treatment may be initiated or continued if TSH levels can be maintained in the normal range by medication. As with other interferons, hypoglycaemia, hyperglycemia and diabetes mellitus have been observed with Peginterferon Alfa-2a. Patients who develop these conditions during treatment and cannot be controlled with medication should discontinue Peginterferon Alfa-2a or Peginterferon Alfa-2a/ribavirin therapy.

Cardiovascular system:

Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with Alfa interferon therapies, including Peginterferon Alfa-2a. It is recommended that patients who have pre-existing cardiac abnormalities have an electrocardiogram prior to initiation of Peginterferon Alfa-2a therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. In patients with cardiovascular disease, anaemia may necessitate dose reduction or discontinuation of ribavirin.

Liver function:

In patients who develop evidence of hepatic decompensation during treatment, Peginterferon Alfa-2a should be discontinued. As with other Alfa interferons, increases in ALT levels above baseline have been observed in patients treated with Peginterferon Alfa-2a, including patients with a viral response. When the increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased direct bilirubin, therapy should be discontinued.

Hypersensitivity:

Serious, acute hypersensitivity reaction (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during Alfa interferon therapy. If this occurs, therapy must be discontinued and appropriate medical therapy instituted immediately. Transient rashes do not necessitate interruption of treatment.

Autoimmune disease:

The development of auto-antibodies and autoimmune disorders has been reported during treatment with Alfa interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed.
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed.

Ocular changes:

Patients with preexisting ophthalmologic disorders (eg, diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during Peginterferon Alfa-2a therapy. Peginterferon Alfa-2a treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

Pulmonary changes:

In case of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment should be discontinued.

Skin disorder:

Peginterferon Alfa-2a must be used with caution in patients with psoriasis, and in cases of onset or worsening of psoriatic lesions, discontinuation of therapy should be considered.

Dental and periodontal disorders:

Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving Peginterferon Alfa-2a and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Peginterferon Alfa-2a and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations.

Colitis:

Ulcerative and hemorrhagic/ischemic colitis, sometimes fatal, have been observed within 12 weeks of starting Alfa interferon teratment. Abdominal pain, bloody diarrhea and fever are the typical manifestations of colitis. Peginterferon Alfa-2a should be discontinued immediately if these symptoms develop. The colitis usually resolves within 1 to 3 weeks of discontinuation of Alfa interferon.

Pancreatitis:

Pancreatitis, sometimes fatal, has occurred during Alfa interferon and ribavirin treatment. Peginterferon Alfa-2a and ribavirin should be suspended if symptoms or signs suggistive of pancreatitis are observed. Peginterferon Alfa-2a and ribavirin should be discontinued in patients diagnosed with pancreatitis.

Pregnancy: (use with ribavirin)

Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking Peginterferon Alfa-2a and ribavirin combination therapy. Women of childbearing potential and men must use two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time.

Nursing Mothers:

Because of the potential for adverse reactions
in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ability to Drive and Use Machines

Patients who develop dizziness, confusion, somnolence or fatigue should be cautioned to avoid driving or operating machinery.

Drug Interactions

Theophylline: Treatment with Peginterferon Alfa-2a once weekly for 4 weeks was associated with an inhibition of P450 1A2 and a 25% increase in theophylline AUC. Theophylline serum levels should be monitored and appropriate dose adjustments considered for patients given both theophylline and Peginterferon Alfa-2a.

Methadone: HCV patients concomitantly receiving methadone treatment with Peginterferon Alfa-2a once weekly for 4 weeks was associated with methadone levels that were 10-15% higher than at baseline. Patients should be monitored for the signs and symptoms of methadone toxicity.

NRTIs: Patients receiving peg interferon-Alfa-2a/ribavirin and NRTIs should be closely monitored for treatment associated toxicities. In addition, dose reduction or discontinuation of Peginterferon Alfa-2a, ribavirin or both should also be considered if worsening toxicities are observed.

Didanosine: Co-administration of ribavirin and didanosine is not recommended.

Zidovudine: Patients who were administered zidovudine in combination with Peginterferon Alfa-2a/ribavirin developed severe neutropenia and severe anemia. Discontinuation of zidovudine should be considered as medically appropriate. Dose reduction or discontinuation of Peginterferon Alfa-2a, ribavirin or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation.

OVERDOSE

There is limited experience with overdosage. There were no serious reactions attributed to overdosages. Dose-limiting toxicities were fatigue, elevated liver enzymes, neutropenia and thrombocytopenia. There is no specific antidote for Peginterferon Alfa-2a. Hemodialysis and peritoneal dialysis are not effective.

STORAGE & INSTRUCTION

Store in the refrigerator between 2^0C - 8^0C.
Do not freeze.
Store in the original pack till in use.
Protect from light.
For subcutaneous use only.

The expiration date refers to the product correctly stored at the required conditions.

Parenteral drug products should br inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

HOW SUPPLIED

UNIPEG (Peginterferon Alfa-2a) 180mcg is available in a unit pack size of 1 Vial along with a sterile syringe and cleansing swab.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

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L00-200004157
Rev. July, 2010